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THE HUXLEY LECTURE

ON

RECENT STUDIES OF IMMUNITY WITH SPECIAL REFERENCE TO THEIR BEARING ON PATHOLOGY.

Delivered at the Opening of the Winter Session of Charing Cross Hospital Medical School on October 1, 1902.

BY WILLIAM H. WELCH, M. D., LL. D.

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You will readily believe that with my deep appreciation of the high honor conferred by the invitation to deliver the fourth Huxley lecture there was joined a sense of great embarrassment in being called upon to follow in this office three such leaders of world-wide fame as Sir Michael Foster, Professor Virchow, and Lord Lister. But the letter of the committee of the Charing Cross Hospital Medical School stated that the choice of a successor to these great names was "a tribute of our admiration for the great army of scientific workers on the other side of the Atlantic." While I cannot assume to occupy any other place in this army than that of a soldier in the ranks, I felt that if my acceptance of this invitation could be regarded as in any sense an expression of appreciation by American workers in science of the commendation and good will of our British colleagues, of our large indebtedness to them, of our sense of the common interests, the comradeship and the kinship of the English-speaking peoples on both sides of the ocean, I would not decline, even if summoned to occupy a position of danger.

There was another consideration which I may be permitted here to mention. Through Huxley there is, if not a bond, at least a link between the Charing Cross Hospital Medical School and the Johns Hopkins University. This lectureship was founded to commemorate the fact that Huxley received his entire medical education at the Charing Cross Hospital Medical School. While throughout America the name of Huxley is held in high honor as that of a great discoverer and interpreter in science, and while the influence which he has exerted upon popular, as well as scientific opinion through those messages peculiarly fitted to the needs of English thought is not less there than among his own countrymen, we at the Johns Hopkins University have special reasons to acknowledge our gratitude to him. He crossed the ocean to deliver the principal address at the opening of this University in 1876, and he then gave utterance to ideas concerning university, and especially medical, education which were at the time and have remained an inspiration and a guide to us. Then, too, the Johns Hopkins University owes to Huxley and to Michael Foster the

accession to its faculty of my lamented colleague, Newell Martin, who by the introduction and development of the biological methods and conceptions of his teachers gave such new directions and so great an impulse to biological study in America that his own work and that of his pupils started for us a new era in this department.

The first Huxley lecturer has made it unnecessary for his successors to dwell upon Huxley's studentship at the Charing Cross Hospital, upon the important influence which this had upon his career, or upon his great services to medical science, although his chief title to fame lies outside of the domain of medicine. I should like, however, to quote a passage, although it must be familiar to you, from Mr. Leonard Huxley's charming "Life and Letters" of his father, which has appeared since the date of Sir Michael Foster's lecture, for it shows that "it was at Charing Cross Hospital where Huxley first felt the influence of daily intercourse with a really able teacher." He says: "No doubt it was very largely my own fault but the only instruction from which I obtained the proper effect of education was that which I received from Mr. Wharton Jones, who was the lecturer on physiology at the Charing Cross School of Medicine. The extent and precision of his knowledge impressed me greatly and the severe exactness of his method of lecturing was quite to my taste. I do not know that I have ever felt so much respect for anybody as a teacher before or since." Wharton Jones, who will doubtless be longest remembered as the discoverer of the amœboid movements of the white blood corpuscles, was an experimental physiologist and pathologist of much originality, and it seems to me that there has not been, even in his own country, so full a recognition of his work as its importance merits.

Before passing to the special theme of this lecture it is fitting that I should pause, if only for a moment, to call to mind with affection and reverence that recently departed great man who honored and delighted you four years ago and who has conferred such high distinction upon the office of Huxley lecturer. When one considers the full import of the discovery and establishment by Virchow of the principles of cellular pathology, that these constitute the secure foundation upon which nearly two generations have built and future generations will continue to build the edifice of scientific medicine, I do not know what greater name there is in the whole history of medicine than that of Rudolf Virchow. How noble his character! With what amazing industry, versatility and keenness of intellect did he fruitfully cultivate the new fields which he had opened to research, as well as other departments of science! With what devotion and beneficial results did he give his time and abundant knowledge to the service of the public and of our profession! We mourn the loss of a hero of medicine and of science, a benefactor of his race, and we rejoice in the rich fruitage of a long and well spent life.

The first place in experimental medicine to-day is occupied by the problems of immunity and, in accordance with the trust of the Huxley Lectureship, which provides that the lecture shall relate to "recent advances in science and their bearing upon medicine and surgery," I have chosen for my theme "Recent Studies of Immunity with special reference to their Bearing on Pathology." As it would be hopeless to attempt a complete review of this broad subject within the space of a single lecture, I shall dwell more particularly upon certain of its aspects, not always of necessity the most important ones, which I conceive to be less familiar to most physicians, or which have engaged my attention, although much which I shall say is of course known to those who have followed the results of recent work in these new lines of investigation.

Under "studies of immunity" I have included, as a matter of convenience, though not with strict accuracy, investigations, which, although the direct outgrowth of those primarily directed toward a solution of the problems of immunity, have extended far beyond these bounds, and have revealed specific properties of cells and fluids in health and in disease of the broadest biological interest. We find illustrated here the familiar fact, nowhere more important to recognize than in medicine, that the sciences are interdependent, that discovery in one field sheds light in the most diverse and often unexpected directions and opens new paths to research. We shall see also exemplified the fructifying influence upon the advancement of knowledge of the discovery and application of new methods of investigation.

In endeavoring to follow in its intimate workings the contest of the living body with its invaders the attention of investigators has naturally been drawn both to the action of the cells and to the properties of the fluids of the body in this struggle, to the latter sometimes without sufficient consideration of the dependence of the humors in their composition upon the cells. Each of these lines of study, whether followed separately or conjointly, has led to the discovery of important facts relating to the mechanism of immunity.

We owe to Metchnikoff and his pupils the most important observations concerning the direct participation of leukocytes and other cells in the processes of infection and the production of immunity. Whatever attitude one may take toward Metchnikoff's well-known phagocytic theory of immunity, one must recognize the wealth of new facts which he has brought to light, and must admire the skill and fertility of resource with which for two decades he has defended this theory against severe assaults, and he has done so, in my judgment, with a large measure of success. With wonderful ingenuity in his recent book on immunity he rescues the phagocytes and applies to a deeper insight into their activities results of his opponents' work.

The other line of research, in some respects more important, was opened by Nuttall in 1888, working in Flügge's laboratory, by his systematic study of the antibacterial properties of the body fluids, particularly of the blood-serum. It is true that there were previous indications of the power of

fresh blood to kill bacteria; indeed, if one wishes to trace this matter historically to its roots, he must go back to John Hunter, who was quite familiar with the anti-putrefactive power of fresh blood, although of course he knew nothing of bacteria. Hunter showed that putrefying fluid could be added in small quantity to fresh blood without setting up putrefaction, and in elaborating his favorite doctrine of the "living principle of the blood" he interested himself greatly in certain phenomena which, interpreted in the light of our present knowledge, are clear anticipations of some recent findings.

After Nuttall our knowledge of the bactericidal power of blood-serum was extended by Buchner and others, but the next advance of fundamental importance in this direction was Pfeiffer's discovery in 1894 of the quick extracellular disintegration and solution of cholera spirilla in the peritoneal cavity of immunized guinea-pigs, or in that of normal guinea-pigs treated with immune serum, and of the presence in the immune serum of a specific substance concerned in the bacteriolytic process, although by itself without bactericidal power.

In the meantime Behring had made his great discovery of antitoxic immunity and of the protective and curative value of antitoxic serum, and Ehrlich had done much to elucidate the nature of this form of immunity. It soon became apparent, however, that immunity from the great majority of bacterial infections does not depend in the main upon the antitoxic principle. The attention of bacteriologists, therefore, was drawn more and more to the so-called "Pfeiffer phenomenon," which was found to be of great general significance, and starting from this and especially from the investigation of the analogous and much more readily studied solution of red corpuscles by foreign serum there has followed in rapid succession up to the present time a series of new and most interesting discoveries and conceptions with which are connected many names, but most prominently those of Metchnikoff and Bordet, and of Ehrlich and Morgenroth.

Through these various studies of immunity we have become acquainted with an important physiological capacity of the healthy organism, the extent and in most instances the existence of which was unsuspected until quite recent years. This capacity is the power to produce substances specifically antagonistic to all sorts of foreign cells and cellular products and derivatives. The substances capable of inducing this immunizing reaction appear to be mainly of an assimilable, albuminous nature, or at least intimately associated with such material, although it has been proved that certain non-albuminous derivatives of proteids have the same power.[1]

The mode of antagonism of the specific bodies formed in response to the reception within the living organism of substances capable of inducing the necessary reaction varies with the nature of these latter substances, and consists in such diverse manifestations as neutralization of poisons and of ferments, injury or destruction of cells, associated with characteristic morphological changes, cessation of motility of cells or their appendages, agglutination of cells, precipitation and coagulation. In accordance with these different effects the corresponding antagonistic bodies, or anti-bodies as they are called, are classified as antitoxins, anti-enzymes, cytotoxins, agglutinins, precipitins, and coagulins, and even against these bodies, with the exception of the antitoxins, antagonists have in turn been produced. All of these bodies are in varying, but usually high degree specific with reference both to the nature and to the source of the material upon which they exert their characteristic effects.

The cytotoxins or cytolysins include not only the bacteriolysins and hæmolysins but also a great number of other cellular toxins present in the sera of animals which have received injections of cells from a different species. To every cellular group of an animal species there appears to correspond a specific cytotoxin. To designate these various cytotoxins such self-explanatory names as leukotoxin, spermotoxin, nephrotoxin, neurotoxin, thyreotoxin, syncytiotoxin are used. Their specificity extends not only to the nature of the cells but also to the species of animal furnishing the cells used for their production.

One of the most important results of recent work is the separation of these specific anti-bodies into two groups, in one of which, represented by the antitoxins, the antagonists are single bodies; while in the other, represented by the cytolysins, the antagonistic effect requires the cooperation of two bodies. Of these two bodies the one which actually destroys the foreign cells or induces other specific effect is normally present in the cells or fluids of the organism, but it seems incapable of action without the intermediation of a body which is distinguished from it by greater resistance to heat and which is produced by the immunizing reaction, although it may also be normally present in smaller amount.[2] The two elements composing a cytolysin exist quite independently of each other, so that one may be present without the other or be artificially removed without affecting the other. Of the multitude of names proposed for these cytolytic components, those most commonly used for the body

[1] Specific precipitins have been produced by injection of crystalline and other so-called pure proteids. Obermayer and Pick produced immune bodies by the use of non-albuminous products of tryptic digestion of certain albumins. Jacoby has shown that the specific body concerned in ricin immunization is non-albuminous. A. Klein obtained entirely negative results with injections of starch, glycogen, glucose, gum arabic, and gelatine.

[2] Metchnikoff believes that the complement or cytase, which in his opinion exists under normal conditions solely within cells, not free in the plasma, acts in natural immunity without the cooperation of an intermediary body or fixative, the latter being concerned only in acquired or artificial immunity. The evidence seems, however, to favor the view that in this regard the conditions are similar in both forms of immunity, the main difference being the presence of a much larger amount of the specific immune body in the latter.

which is the specific product of immunization, although it may also exist normally, are intermediary body, immune body, amboceptor, sensitizer, fixative, preparative, copula, desmon, and for the other body complement, alexin, cytase. It is this latter body which contains the atomic group described as toxophoric or zymophoric.

Concerning the source, mode of action, and constitution of the specific antagonistic bodies we are very imperfectly informed. That they are of cellular origin seems certain and Ehrlich with great ingenuity on the basis of a brilliant series of experiments has advanced an hypothesis regarding them, which, in my opinion, better than any other hitherto suggested accords with the known facts and in promoting discovery has already done the greatest service of which a working hypothesis is capable. Ehrlich has so recently and so fully in the Croonian lecture presented before English readers his hypothesis of the side-chains or receptors and the basis for it, that I need only recall to your minds his conception that the toxins, cells and other substances which lead within the living body to the production of antitoxins, cytolysins, and other antagonists have this capacity only through the possession of specific affinities, called haptophore groups, for corresponding haptophore groups belonging to side-chains or receptors of certain cellular constituents of the body, and that, in consequence of this appropriation of receptors, others of like nature are reproduced in excess of the needs of the cell, and these being shed into the lymph and blood there constitute the antitoxins, intermediary bodies, agglutinins and other specific antagonists. The antitoxic receptor has only a single combining affinity, which is for the toxin; whereas the cast-off receptors constituting the intermediary bodies of cytolysins have at least two affinities (hence called amboceptors by Ehrlich), one of a more highly specialized nature being for the invading bacteria or other foreign cells, and the other for the complement.[3] The anti-body enters quantitatively into definite chemical union with its affinitive substance.

The essence of Ehrlich's theory concerning antitoxin is thus tersely expressed by Behring: "The same substance which, when incorporated in the cells of the living body, is the prerequisite and condition for an intoxication becomes the means of cure when it exists in the circulating blood." So of the twofold bactericidal and cytolytic agents we may say that the living body possesses substances which may protect it by destruction of invaders or may injure it by destruction of its own cells according to the mates with which these substances are joined.

An inquiry which naturally arises in this connection is: What is the physiological mechanism called into action in the processes resulting in the production of antitoxins, cytolysins, and similar bodies? We have no reason to suppose that the animal body is endowed with properties specially designed to meet pathological emergencies. Its sole weapons of defense, often lamentably imperfect for morbid states, are adapted primarily to physiological uses.[4] To the foregoing inquiry Ehrlich answers that the mechanism concerned is one physiologically employed for the assimilation by the cells of food. The receptors are in the cells not for the purpose of linking poisons to the cells but to seize certain food-stuffs, particularly the proteids, and the toxins and bacterial and other foreign cellular substances, if capable of inducing the immunizing reaction, chance to have the requisite combining affinities for the food-receptors. It is interesting that Metchnikoff also, though from a different point of view, refers the mechanism of immunity to the physiological function of assimilation of food by the cells.

Inasmuch as according to Ehrlich's hypothesis the specific antagonistic substances resulting from the injection of toxins and of foreign cells or derivatives of cells exist preformed in cells of the normal body, there would appear to be no reason why anyone of them might not occasionally be present normally free in the blood or fluids. In fact many of them, such as diphtheria and tetanus antitoxins, various anti-enzymes, bactericidal, hæmolytic and other cellular toxins, agglutinins and a number of other bodies of this class, as well as their anti-bodies, have been found repeatedly, though of course in the case of many inconstantly and with marked differences between individuals and species, in the blood of healthy human beings or animals when their presence could not reasonably be attributed to a previous specific immunization. Of these normal anti-bodies the only one which is increased in amount by the process of immunization is that specifically related to the material used to bring about the reaction. As already stated it is the intermediary body,[5] not the complement, which is generated in immunization against bacteria and other cells.

The foregoing statements, though of necessity condensed and incomplete, about the general characters of the specific anti-bodies will, I trust, help to a better understanding of what is to follow concerning the bearing of some of these discoveries on medical science and practice. I realize the difficulties which you must already have experienced, if un-

[3] According to Ehrlich's latest conception resulting from investigations to demonstrate the multiplicity of complements an amboceptor has a single cytophilic affinity and a number of complementophilic affinities differing in their avidity for various complements. He regards the agglutinins, precipitins and coagulins as uniceptors of more complex structure than the antitoxins, but Bail has recently brought evidence to show that agglutinins, like cytolysins, are composed of two elements. For the purposes of this lecture it is not deemed necessary to enter into these or many other details of this complicated subject. For comprehensive and admirable critical reviews of recent theories of immunity and Ehrlich's hypothesis of the receptors I would refer to Dr. Ritchie's papers in "The Journal of Hygiene," Vol. II, Nos. 2, 3 and 4, and to Dr. Aschoff's paper in Zeitschrift f. allgem. Physiologie, Bd. I, Heft 3, Jena, 1902.

[4] W. H. Welch: Adaptation in Pathological Processes. Trans. Congress American Physicians and Surgeons, 1897, Vol. IV.

[5] I use in this lecture the name "intermediary body" in preference to the more technical term "amboceptor," although Ehrlich applies the German equivalent—Zwischenkörper—only to normal as distinguished from immune amboceptors.

familiar with these new lines of research, in following a brief presentation of a subject in which not only are the facts so complex and the ideas so novel, but the terminology so strange and burdened with such a multitude of confusing synonyms. While deploring the multiplication of unnecessary new terms, I should like to quote in this connection a wise remark of Huxley:[6] "If we find that the ascertainment of the order of nature is facilitated by using one terminology, or one set of symbols, rather than another, it is our clear duty to use the former; and no harm can accrue so long as we bear in mind that we are dealing merely with terms and symbols."

The most remarkable and characteristic attribute of these anti-bodies is the specificity of their relation to the substances which have led to their formation. Of some of them, such as diphtheria or tetanus antitoxin this specificity is nearly absolute; of others, such as the precipitins, it is only relative. This property is the basis of new and most valuable methods for the identification of species and the determination of genetic relations—species not only of living things, but also of chemical substances and of disease.

The resemblances and the differences thus revealed are doubtless fundamentally of a physico-chemical nature, but in many instances they transcend the powers of the microscope or of ordinary chemical tests to detect.

The results already attained by the method of serum diagnosis,[7] using this expression in its widest sense, are not only of interest and importance to the biologist, physiologist, and chemist, but of great practical value to the bacteriologist and the physician. As this is not an aspect of my subject, broad and important as it is, upon the details of which I propose to dwell, it must suffice to present by way of illustration examples of the diagnostic application of different kinds of specific sera.

The only certain means of detecting toxins of the class of diphtheria or tetanus toxin, snake venom, and certain vegetable poisons of the same category is their neutralization by the corresponding antitoxic sera. Occasion may arise where such detection is of practical and even medico-legal importance, as has been exemplified in India, where the criminal use of cobra venom is not unknown.

The application of serum diagnosis which is most familiar to physicians is the agglutinative test for typhoid fever. The principles of the agglutinative reaction were worked out in the laboratory of Professor Gruber in Vienna by himself and Durham and were there first applied to the diagnosis of typhoid fever by Grünbaum, who was anticipated in his publication by Widal, who has made a thorough clinical study of the subject. The method is of great value not only in the diagnosis of disease but also in the identification of bacterial species and the recognition of relationships between species. Durham, to whom we owe important contributions to this subject, has given an ingenious hypothetical explanation of mutual agglutinative reactions, the main features of which are paralleled in Ehrlich and Morgenroth's doctrine, based upon experiments, relating to the multiplicity of cell-receptors and of amboceptors concerned in hæmolysis.[8]

We have found the agglutinative reaction an indispensable aid in the study of the series of cases of paratyphoid fever which have come under observation in Dr. Osler's wards at the Johns Hopkins Hospital, and which otherwise it would have been scarcely possible to have separated from typhoid fever.[9] The occurrence of paratyphoid fever as a distinct disease affords an explanation of a certain proportion of the failures of the serum from supposed typhoid-fever patients to clump typhoid bacilli. Not less valuable is the serum test in the diagnosis of *Bacillus dysenteriæ* Shiga and of the diseases caused by it. This microörganism has been shown by Flexner and his pupils, Vedder and Duval, to be the cause of our acute dysenteries, and recently in Baltimore Duval and Bassett, working with the aid of the Rockefeller Institute for Medical Research at the Thomas Wilson Sanitarium, have discovered that this same bacillus is probably the specific agent of infection in the summer diarrhœas of infants.

Bacteriolytic sera have been used by Pfeiffer in the differentiation of cholera and allied spirilla, but few other bacteria present equally well the Pfeiffer reaction, which is not nearly so useful or handy a means of identification as the Gruber-Durham reaction.

Of other cytolytic sera the hæmolysins have been by far the most carefully studied. One of the most interesting results of this study has been the determination by precise quantitative methods of resemblances and of differences between red blood corpuscles which in no other way could be distinguished. These resemblances and differences relate not only to the red corpuscles of different species of animals, but also to those of individuals of the same species. Although we constantly assume the existence of cellular differences between individuals and between species, these are for the most part of so subtile a nature as to elude our methods of observation. The exact demonstration of such differences

[6] Huxley: On the physical basis of life. Collected Essays, Vol. I, p. 164, New York, 1893.

[7] The general procedure followed in the production of specific sera is the injection into a suitable animal at intervals of time repeated doses of toxins, bacteria, foreign cells or other material against which the anti-body is desired. For example if a specific precipitating or a hæmolytic serum for human blood is wanted, an animal, say a rabbit, is injected subcutaneously or intraperitoneally at intervals of three or more days with five or six doses of human serum or human red blood corpuscles. At the end of this time the rabbit's serum has acquired the property of precipitating human serum in strong dilutions, or of dissolving human red blood corpuscles, if these were used for the injection. Within limits the less closely related the two species of animals, the more powerful is the antagonistic effect of the specific serum. This is true especially in the case of cytotoxic sera.

[8] Durham: Journal of Experimental Medicine, Jan. 15, 1901, Vol. V, p. 353. Ehrlich and Morgenroth: Berliner klin. Wochenschr., May 27, 1901, p. 670.

[9] See papers on paratyphoid fever by Johnston, Hewlett, and Longcope in American Journal of Medical Sciences, August, 1902.

by the use of cytolytic sera is, therefore, of especial interest. My assistant, Dr. H. T. Marshall, in an unpublished research, conducted under the direction of Professor Ehrlich and Dr. Morgenroth, upon the receptors of the red blood corpuscles of man and of two species of monkey found that while man and the monkeys each has receptors not shared by the other they also have a large number of receptors in common.

This result is in harmony with Nuttall's interesting observations on a much more extended scale regarding phylogenetic relationships between animal species as shown by the reaction of their blood with the specific precipitins discovered by Tchistowitch and Bordet and introduced into practical medicine by Wassermann. This biological test to determine the source of blood, when used with proper precautions, far surpasses in accuracy all other methods for this end. While it would lead too far from my purpose to follow this subject farther, I cannot in this connection forbear at least mentioning one of the earliest and most suggestive papers on this class of anti-bodies, that "On Immunity against Proteids" by Walter Myers, who gave up his life in the cause of science and of humanity and whose early death is so great a loss to English medical science.

I shall ask your attention now to some considerations concerning the bearing of recent studies of immunity on the nature and action of toxins. This subject is of course of the greatest pathological as well as bacteriological importance, and I believe a closer cooperation than now exists between bacteriologists and pathologists in its study would further the surer and more rapid advancement of our knowledge about it. One misses only too often in purely bacteriological papers on this subject exact knowledge and descriptions of pathological conditions, and on the other hand pathologists often fail to utilize pertinent facts and ideas which are familiar to bacteriologists.

The discovery by Roux and Yersin of the diphtheria toxin, the studies by Behring and Kitasato of tetanus toxin leading up to Behring's epochal discovery of antitoxin, and the later investigations of Ehrlich on the constitution of diphtheria toxin and the origin and mode of action of antitoxin are the great events in the most brilliant and securely founded chapter of modern studies of immunity. Through these researches we became acquainted with a class of poisons secreted by certain bacteria and present in solution in culture fluids. The evidence is conclusive that these soluble toxins enter, as assimilable substances, into direct combination with constituents of the body cells for which they have an affinity, and only thereby are enabled to bring about immunity or to exert toxic effects. As shown by the modifications of toxins called toxoids, the toxic property may be lost without loss of the combining power and without removal of the immunizing power. According to Ehrlich's helpful conception, based on a large amount of experimental evidence and now generally accepted, the combining power of the toxin molecule resides in a group of atoms, designated as the haptophore group, with affinity for the corresponding haptophore groups of the side-chains or receptors of cellular constituents, and the toxic power pertains to another and less stable atom-complex in the molecule.

By means of these facts and legitimate deductions from them we are enabled to explain in a satisfactory way susceptibility to poisoning by these soluble toxins, their selective action upon the cells of the body, and their quick disappearance after injection into the circulating blood. In one infectious disease and in one only, to wit tetanus, are we able to explain the clinical and pathological phenomena in minute detail on the basis of our knowledge of the causative microörganism and its poisonous products. The nearest approach to this instance is diphtheria, but here we have not yet been able to follow the trail of the toxins within the body so perfectly, and, as Flexner and I have shown, in addition to the soluble toxins there is an intracellular poison concerned in the production of the false membrane. Interesting investigations, which have greatly helped to elucidate the nature of these toxins, have been made on various similar vegetable and animal poisons, such as ricin and abrin from the former source and the venom of snakes, spiders and other poisonous animals.

The high hopes which were raised by the discovery of the soluble bacterial toxins that at last the way was opened for us to penetrate into the mysteries of the mode of action of pathogenic bacteria were soon doomed to disappointment, for similar powerful toxins, though diligently sought, could not be detected in the cultures of most other bacteria, and these among the most important ones, such as the tubercle bacillus, the typhoid bacillus, the cholera spirillum, the pneumococcus, the pyogenic micrococci. This disappointment was all the more acute because there was and is every ground for confidence that whenever we have in our possession a powerful toxin of this class, a strong protective antitoxic serum can readily be obtained.

Notwithstanding these negative results the belief was not abandoned that bacteria harm the body mainly by poisoning, for it rests upon strong clinical and pathological evidence, as well as upon the study of the distribution of bacteria in the infected body. The search for poisons was turned from the fluid part of cultures to the bacteria themselves and thus Pfeiffer succeeded in demonstrating as an integral constituent of the bodies of cholera spirilla toxic substances, which are liberated only when the bacteria degenerate or die. Intracellular poisons, which indeed previously, though of a different nature, had been extracted from bacteria by Buchner and by Koch, were subsequently found within typhoid bacilli and a number of other pathogenic bacteria.

It is of more than purely bacteriological interest to recognize the distinction between the small group of pathogenic bacteria, represented by the bacilli of tetanus, of diphtheria, and of botulism, characterized by the secretion of powerful soluble toxins, and the much larger group, containing most of the other pathogenic bacteria, which do not secrete similar strong toxins, for it is only the former which give rise to

the production of antitoxic sera of marked protective and curative power.

The form of immunity resulting from injections or natural infections with the second class of bacteria belongs mainly to the bacteriolytic type, in which the complete anti-body is not a single substance, like antitoxin, but is composed of two distinct elements, intermediary body and complement, of which only the former is produced or increased in the process of immunization. The bacteriolytic sera are also under suitable, but not readily controlled conditions protective and curative, but owing, it would seem, mainly to the duplex nature of the anti-body their successful therapeutic application meets difficulties which have not yet been overcome. The great practical problem of bacteriology to-day is to make available to medical practice the bacteriolytic sera, such as anti-typhoid, anti-pneumococcus, anti-streptococcus, anti-plague, anti-dysentery sera. Such work as that of Marmorek, of Wassermann, of Neisser and Wechsberg, of Ainley Walker upon the production, the properties, the conditions underlying the action of these sera is, therefore, highly important.

Our knowledge of the constitution and action of the intracellular bacterial poisons is most incomplete and at present cannot be applied in any very definite and satisfactory way to the explanation of the morbid phenomena of infectious diseases. Such investigations as those undertaken by Macfadyen and Rowland at the Jenner Institute of Preventive Medicine upon the expressed juices of bacterial cells promise to shed light upon this subject and in general upon the vital processes of bacteria. The recent researches of Vaughan and his collaborators upon intracellular bacterial toxins are also most valuable.

I find it difficult to reconcile myself to the doctrine that bacteria such as the typhoid bacillus, the pneumococcus, and others of the class now under consideration do their chief injury to the body, not while they are lively and vigorous, but after they become corpses and in consequence set free their protoplasmic poisons. Still this latter conception is the basis of a coherent hypothesis of infection, elaborated most fully recently by Radzievsky,[10] which rests upon a considerable amount of accurate observation and interesting experimental work. There can be no doubt that in the course of many infections there goes on an enormous destruction of the bacteria concerned, so that the numbers of those indicated at any given time by microscopical examination and by cultures may represent only an insignificant fraction of the total progeny of the first invaders. I have been much interested in this phenomenon since I became familiar with it over twelve years ago[11] in pneumococcus infections through the employment of a method which revealed in the exudates degenerating and dead pneumococci and their empty capsules in numbers often far exceeding the intact organisms, indeed in some cases so many that they formed a large part of the exudate.

While all due weight should be given to such facts as these the objections to the acceptance of the hypothesis just mentioned as affording a complete explanation of the toxic phenomena of this class of infections are so obvious that naturally efforts have been made to learn whether bacteria which produce no strong soluble toxins in our ordinary culture media may not do so on other media of special composition or in a demonstrable way within the living body. Work in these two directions has not been altogether barren as shown by results of experiments made by Hueppe, Cartwright Wood, Marmorek, and others, along the former lines, and by Metchnikoff, Roux and Salimbeni along the latter, but it cannot be said that these experiments have led to any generally accepted solution of the main difficulties. Some are therefore inclined to lay the chief emphasis upon disordered cellular metabolism, but this is only a restatement of the question. Everybody recognizes abnormal metabolism as an essential condition in infections. The very point needing explanation is how the bacteria derange metabolism.

I wish here to advance an hypothesis which seems competent to explain the source, the mode of production, and the nature of certain bacterial toxins. It would appear to be a natural inference from the receptor theory of Ehrlich and the recent work on cytotoxins. The following considerations will, I hope, make clear the essential points.

As I have already stated, we know that the injection of foreign cells, such as pathogenic bacteria, red blood corpuscles, spermatozoa, epithelium, into the tissues of a living animal leads to the formation of poisons, called cytotoxins, acting specifically upon these cells; that the substances which stimulate the cells of the host to produce one constituent of this class of toxins consist of certain atom-complexes derived from the injected cells; that certain cells of the host thus stimulated generate and discharge one component of the toxin, called the intermediary body, which becomes the medium of intoxication through union, on the one hand, with a pre-existent toxophore substance, called the complement, and, on the other hand, with the foreign cell which started the reaction.

Such is the response on the part of the host to the entrance of the foreign cells, but how about a possible response of a like nature on the part of the invading cells toward the host, resulting in the production of special cytotoxins, of analogous constitution, injurious to the host? This latter response, being of a vital nature, can take place only when the invading cells are living, as in the case of bacteria and other parasites. I see no reason why suitable substances derived from the host may not stimulate parasitic organisms, through a physiological mechanism similar to that operative in the development of cytolytic immunity, to the production of intermediary bodies, which, if provided with the requi-

[10] Radzievsky: Zeitschrift für Hygiene, 1900, XXXIV, p. 369, and 1901, XXXVII, p. 1.

[11] Welch: Bulletin of the Johns Hopkins Hospital, July, 1890, and December, 1892. Michaelis (Berliner klin. Wochenschr., 1902, No. 20) has recently reported similar findings.

site affinities, have the power to link complements to cellular constituents of the host and thereby to poison the latter. Expressed in terms of Ehrlich's side-chain theory, certain substances of the host of cellular origin, assimilable by the parasites through the possession of haptophore groups with the proper affinities, become anchored to receptors of the parasitic cell, which, if not too much damaged, is thereby stimulated to the over-production of like receptors; these excessive receptors of the parasite, if cast off into the fluids or the cells of the host, there constitute intermediary bodies or amboceptors with special affinities for those cellular constituents or derivatives of the host which led to their production and for others which possess in whole or in part identical receptors. Provided the host is supplied also with the appropriate complements there result cytotoxins with special affinities for certain definite cells or substances of cellular origin in the host. The contribution of the parasitic cells to these cytotoxins is the amboceptors. Either the parasite or the host may provide the complements.[12]

It may perhaps aid in grasping the ideas here presented to imagine the bacterium, in the capacity of the host, as a structure so large that one could inject into it animal cells. Provided the proper receptor apparatus is present, the resulting reaction on the part of the bacterium, as described, would be a process of immunization against the animal cells through the formation of specific cellulicidal substances. In reality it is only certain atomic complexes of cells which are concerned in this immunizing reaction, and in comparison with these even the smallest bacterium is a gigantic object.

Looked at from the point of view of the bacterium, as well as from that of the animal host, according to the hypothesis advanced, the struggle between the bacteria and the body cells in infections may be conceived as an immunizing contest in which each participant is stimulated by its opponent to the production of cytotoxins hostile to the other and thereby endeavors to make itself immune against its antagonist. These mutually antagonistic cytotoxins are capable of injuring the parasitic cells, on the one hand, or the body cells, on the other, only when, escaping combination outside of them, they are anchored to the receptors of the cells to which their respective affinities are adjusted. This combination with the cells, if it does not result in too great injury to them, is the condition for further production of the cytotoxic intermediary bodies through overproduction and discharge of receptors.[13] The important factors determining the issue of the contest are the nature, the relative proportions and the distribution of the bacterial cytotoxins and the host's cytotoxins respectively.

The hypothesis thus outlined can be tested experimentally, but I regret that it has shaped itself in my mind so recently that I have not yet been able to make the desired experiments, which are, however, now started in my laboratory. Since my arrival here I am informed that these experiments have already furnished facts in its support.

Inasmuch as at least one component, and it may be both components, of the assumed bacterial cytotoxins preexist in the bacterial cells, it should be possible to demonstrate some of them in artificial cultures of bacteria, where they would be found especially as integral parts of the cells, unless extracted from the bodies of degenerating or dead bacteria. This corresponds with what is known concerning the situation of the poisons of the cholera spirillum, the typhoid bacillus, and other bacteria characterized by the lack of strong soluble toxins. But the quantitative and other relations between these cultural cytotoxins and those produced, in the manner described, by the same bacteria during processes of infection are comparable to those between the normal anti-bodies and the immune anti-bodies. These relations would explain the familiar fact that cultures of bacteria of the class under consideration constitute in general only a partial and meagre index of the toxic capacities of the same bacteria in the infected body. That cytolysins may, however, be present normally in large amount is illustrated by the hæmolysins of eel's serum and of snake venom.

[12] We may thus speak of somatogenic cytotoxins resulting from the action of bacterial stimuli on cells of the host, and of bacteriogenic cytotoxins from somatogenic stimuli, also of somatogenic and bacteriogenic complements.

[13] It will be observed that these discharged receptors may be regarded as the equivalents of anti-immune bodies. E. W. Ainley Walker, in an interesting and suggestive paper on "Immunisation against Immune Serum" (Journal of Pathology and Bacteriology, March, 1902), shows experimentally that bacteria growing in immune sera produce anti-immune bodies and thereby become more virulent. He concludes that "the basis of bacterial virulence and of chemiotactic influence is identical, and constitutes that atom group which causes the production of the immune body." My hypothesis includes the conception supported by Walker and also much more. According to the hypothesis certain anti-bodies of bacterial origin are capable not only of neutralizing immune bodies of the host but with the aid of complements also of poisoning the cells of the host. It is not difficult to imagine various conditions in which the anti-bodies of bacterial origin may escape neutralization before entering into union with the host's cells. The substances which stimulate bacteria to produce these anti-bodies need not necessarily be toxic to them; in fact toxicity, such as that of strong bactericides of cellular origin, would hinder their production. The essential things are that the stimulating substances have the requisite combining groups for bacterial receptors, and that the cast off receptors be complemented within the body of the host.

Each of the various bacteriogenic cytotoxins probably contains a multitude of partial amboceptors with varying cytophilic and complementophilic affinities, in accordance with the views of Ehrlich and Morgenroth.

It is self evident that through a mechanism similar to that described parasites within the infected body may be stimulated by atomic groups derived from the host to the production also of anti-bodies other than complex cytotoxins, such as various agglutinins, precipitins, anti-enzymes, and perhaps of uniceptors of the nature of secreted, soluble toxins, or of enzymes, all adjusted against the host.

Questions relating to the source and nature of the complements, particularly of intra-cellular complements, and also to anti-complements, are manifestly of importance in relation to the hypothesis, but it would complicate the subject too much to discuss these and other matters here, where my purpose is merely to outline the essential features of this new theory of infection with reference to the particular points under consideration.

In this theory degenerated and dead bacteria, while recognized as a source of poisoning in infections, are not assigned an exclusive rôle in this regard. Living bacteria in the infected body, where they are under nutritive conditions not paralleled in artificial cultures, actively produce and secrete receptors which may become the means of intoxication of the body cells. From what has been said, we can comprehend how these diverse free receptors may enter into the formation of cytotoxins of the most varied and specific characters, such as erythotoxins, leukotoxins, neurotoxins, nephrotoxins, spermotoxins, hepatotoxins, etc. Very probably in many instances these toxins are represented by so few receptors in bacterial cells in ordinary cultures, that it would be hopeless to search for them there, although we may have convincing experimental and pathological evidence that within the animal body the same bacteria produce them abundantly under the stimulus of appropriate substances derived from cells of the host.

The methods hitherto employed for the study of bacterial poisons have not generally been calculated to reveal the presence of toxins with the characters indicated, even if such existed in the cultures. Recently, however, a beginning has been made in this direction, and we have already become acquainted with certain toxins of an interesting nature, to which I desire to direct your attention.

Intrinsically and in their general bearing upon the subject before us the recent investigations of Flexner and Noguchi upon the constitution of the toxins in snake venom are of especial importance. It was in snake venom that Weir Mitchell and Reichert first demonstrated the existence of that class of poisons often called, although with doubtful propriety, toxic albumins. Investigations of snake toxins are of peculiar interest for many reasons, not the least of which is their resemblance to bacterial toxins. The demonstration by Sewall of the possibility of active immunization from venom and the further studies by Calmette and Fraser of this phenomenon and especially of the protective and curative properties of antivenin are well known.

Until recently it has been generally held that the venom toxins resemble in molecular structure the diphtheria and the tetanus toxins in being single bodies with a combining or haptophore group and a toxophore group of atoms. The researches of Flexner and Noguchi, now in progress, of which only the first part has been published,[14] necessitate a quite different conception of the nature and manner of action of venom toxins than that previously entertained. I have followed with great interest the work of Professor Flexner on toxins, begun several years ago in my laboratory when he was my assistant and associate, and since continued along new lines in his laboratory at the University of Pennsylvania and I wish to acknowledge his generosity in permitting me to use in this lecture certain unpublished results of his and Noguchi's investigations.

These investigations have shown that the toxic action of venom upon red blood corpuscles, leukocytes, nerve cells, and other cells is like that of the duplex cytotoxins already described; that is, it depends upon the combination of intermediary bodies contained in the venom, on the one hand with the animal cells for which these bodies respectively have affinities and on the other hand with corresponding complements contained, not in the venom, but in the cells or fluids of the animal acted on. For example, it is well known that the addition of venoms to fresh blood brings about the quick destruction and solution of the red corpuscles. If, however, certain venoms be added to red corpuscles which have been thoroughly washed with isotonic salt solution so as to remove all the complement, the corpuscles are agglutinated but not dissolved, although it can be shown that substances from the venom (intermediary bodies) have entered into combination with the corpuscles. If now a little fresh serum which contains the complement and by itself may be an excellent preservative of normal corpuscles, be added to these venomized corpuscles, they are promptly dissolved.

Preston Kyes, working in Professor Ehrlich's laboratory, in an investigation just published[15] on the mode of action of cobra venom, confirms the conclusion of Flexner and Noguchi concerning the amboceptor nature of cobra venom, and adds much that is new and important to our knowledge of this subject. He finds that the washed blood corpuscles of certain animals are directly dissolved by cobra venom, while those of other animal species require the subsequent addition of complements or adjuvants to bring them under the influence of the venom. But even in the former case a complementary body is essential to the reaction, this, however, being not a serum complement but an endocomplement contained within the red corpuscles. Of great significance is the demonstration by Kyes of still a third substance, namely lecithin, which is capable through combination with the venom intermediary body of completing the hæmolytic potency of venom.[16] The discovery for the first time of a definite, crystallizable substance with the power of uniting, like a complement, with an intermediary body and thus completing the formation of a cytotoxin is evidently of fundamental importance. The suggestion by Ehrlich and Kyes that possibly the cholin group is the toxophore group of lecithin is particularly interesting in the light of F. W.

[14] Flexner and Noguchi: Snake venom in relation to hæmolysis, bacteriolysis and toxicity. Journal of Experimental Medicine, March 17, 1902, Vol. VI, p. 277.

[15] Preston Kyes: Ueber die Wirkungsweise des Cobragiftes. Berliner klin. Wochenschr., 1902, Nos. 38 and 39. I am greatly indebted to my friend Professor Ehrlich and to my former pupil Dr. Kyes in putting me in possession of the main results of these interesting experiments before their publication.

[16] The objections made by Calmette (Compt. rend. Acad. d. Sc., 1902, T. 134, No. 24) to Flexner and Noguchi's interpretation of their experiments as to the amboceptor nature of venom have been completely overthrown by the experiments of Preston Kyes.

Mott's valuable studies of chemical processes concerned in degenerations of the nervous system.

The researches of Flexner and Noguchi and of Kyes therefore have taught us that in poisoning by venom the bodies of human beings and of animals contain in the form of complements, or alexins[17] as they are also called, the substances which are most directly concerned in the act of poisoning. The venom brings into the necessary relations with constituents of the body cells poisons we already harbor or may generate but which are harmless without the intervention of intermediary bodies. These poisons within us are powerful weapons, which, when seized by hostile hands, may be turned with deadly effect against our own cells, but which are also our main defense against parasitic invaders.

Flexner and Noguchi have demonstrated experimentally that, like the hæmolytic, so also the leukotoxic, the neurotoxic, and other cytotoxic properties of venom depend upon combinations of venom intermediary bodies with complements contained in the cells poisoned by venom or in the fluids bathing these cells. Particularly striking are their experiments showing in vitro and under the microscope the cytolytic action of cobra venom upon certain large molluscan nerve cells in the fresh state. The complement essential to this reaction is contained within the nerve cells. In previous experiments of Flexner and Noguchi there had been indications that intracellular complements are concerned in some of the toxic effects of venom upon cells. The positive demonstration by Preston Kyes of a special class of intracellular complements or endocomplements is unquestionably of great pathological interest, and seems destined to play an important part in the explanation of many morbid conditions in connection with endogenic and exogenic intoxications, probably also in such phenomena as self-digestion or autolysis.

Snake venom is a rich mine of diverse toxins, and, on account of its pathological importance, I must mention one of the cytotoxins discovered there by Flexner and Noguchi, as it may be that a similar toxin is produced by certain bacteria and under still other conditions. As is well known, one of the most striking lesions resulting from poisoning by certain venoms is the occurrence of abundant hæmorrhages in various tissues of the body. This effect has been generally attributed to the direct action of venom on the red corpuscles and on the coagulability of the blood, but the experiments of Flexner and Noguchi indicate that these hæmorrhages are due to the presence in venom of a cytotoxin which has the power of dissolving endothelial cells, in other words an endotheliolysin. Dr. Flexner suggests the name "hæmorrhagin" for this special toxin which causes extravasations of blood through its direct solvent action upon capillary endothelium, an effect which is readily demonstrable under the microscope. It is hardly necessary for me to stop to emphasize the clinical and pathological importance of the discovery of an endotheliotoxin, a kind of poison which may prove to be of special significance in the interesting group of hæmorrhagic infections and perhaps also in purpura and kindred affections.

The foregoing newly discovered facts, which I have sketched only in bare outline, illustrate in a striking way the fruitfulness of methods and conceptions which we owe to recent studies of immunity. The results of these investigations, however, are significant beyond the mere facts disclosed, important as these are. They have for the first time revealed in normal toxic secretions, readily introduced under conditions of nature into the tissues of man and animals, cellular poisons akin to the complex hæmolysins, neurotoxins and other cytotoxins of immune and some normal sera, which have aroused so much interest and experimental study during the past four years. The most noticeable difference between the venom cytotoxins and those hitherto observed in immune sera is the far greater resistance to heat of the intermediary bodies of the former, but we are already acquainted with considerable variations in the sensitiveness to heat both of different intermediary bodies and of complements. That snake venom should contain only one-half of the complete poison, the other and the really destructive half being widely distributed in the blood and cells of man and of animals, is an instance of a curious kind of adaptation, of interest from evolutionary as well as from other points of view.

In consideration of the often emphasized analogies between venom toxins and bacterial toxins, these facts render it highly desirable to make a systematic search of bacterial cultures by proper methods and under suitable conditions for complex cytotoxins. At present substances of this nature are not known to exist in our cultures. There have been discovered, however, within the past three or four years certain bacterial toxins which have a curious resemblance in some of their properties to the complex antibodies of blood, although, so far as they have been carefully studied, they appear to have the simpler constitution of the soluble toxins, like those of diphtheria and of tetanus. I refer to the bacterial hæmolysins, leukolysins, hæmagglutinins, precipitins and coagulins. There is no reason to suppose that this list exhausts the number of those actually present, for it is evident that it includes chiefly bodies readily demonstrable in test-tube experiments. It would be surprising if cytotoxins which act specifically upon red and white blood corpuscles were the only ones of this class produced by bacteria; in fact we have every reason from pathological observations to believe the contrary.

It has become evident that more refined methods than mere observation of the coarse effects of injecting into animals the filtrates or the killed bacteria of our cultures are required for the detection of the subtler and more specific cellular poisons. Instances are rapidly increasing in which

[17] There is some objection to the use of the term "alexin" as a synonym for "complement," as the former was applied originally by Buchner to substances which we now know to be combinations of complements with intermediary bodies.

by improved methods cultures of bacterial species once believed to be practically devoid of toxicity are found after all not to be so poor in toxins, even of the soluble variety. One of the earliest and most instructive illustrations of this is the discovery by Van De Velde of a leukocyte-destroying poison, named leukocidin, in exudates caused by infection with *Staphylococcus aureus* and also in filtrates of staphylococcus cultures, which had been previously regarded as almost entirely free of toxic power.

More widely distributed in cultures of different species of bacteria are the hæmolysins, of which the first example, discovered in 1898 by Ehrlich in cultures of the tetanus bacillus, was carefully studied by Madsen the following year, and which have since been investigated by Kraus with Clairmont and with Ludwig, Bulloch and Hunter, Neisser and Wechsberg, Todd, Besredka, and others. The list of bacterial species known to produce in cultures substances of this nature capable of dissolving red blood corpuscles is already a long one and includes the bacilli of tetanus, of green pus, of typhoid fever, of acute dysentery, of diphtheria, of plague, the pyogenic staphylococci and streptococci, the pneumococcus and many other bacteria. Nuttall and I noted in our first description of *Bacillus aërogenes capsulatus* over ten years ago its capacity of laking blood so that I was not surprised to find recently that an hæmolysin can be demonstrated in cultures of this organism. The blood-destroying property appears to stand in no definite relation to virulence, nor is it limited to pathogenic bacteria. It pertains also to many putrefactive bacteria. The strongest bacterial hæmolysin hitherto observed was found by Todd in cultures of *Bacillus megatherium*, which is a widely distributed saprophyte.

As already stated, none of these bodies has been shown to belong to the class of complex hæmolysins in blood, which have been far more exhaustively investigated than any other of the specific anti-bodies. Doubtless there is at present among bacteriologists too great a tendency to attribute to the less carefully studied anti-bodies characters which have been worked out in detail only for the hæmolysins of immune serum. It would lead too far to attempt here a discussion of the special characters of the various bacterial hæmolysins, which present in different specimens curious and at present unexplained divergencies as regards resistance to heat and several other properties. It must suffice to indicate briefly what is known of the pathological importance of this interesting group of bacterial toxins.

In view of the abundant clinical and pathological evidence of extensive destruction of red corpuscles in the course of many infectious diseases, it is certainly significant to find that many bacteria are endowed with a specific hæmolytic power. The question is how far we are justified in applying to the actual conditions of infection the existing experimental data upon this subject. Assuredly here, as everywhere, results of test-tube experiments, helpful in suggestion as they may be, should not be utilized without further evidence to explain morbid phenomena within the infected human or animal body. While much more work upon this subject is needed before our information will be exact or complete, the observations and experiments of Besredka,[18] Kraus and Ludwig[19] and others have already demonstrated that bacteria may exert their blood-destroying power within the living body. This hæmolytic capacity of microörganisms affords an explanation, although certainly not the only one, of the secondary anæmias which are such a marked feature of many infectious diseases, as streptococcic and other septicæmias, pneumonia, typhoid fever, scarlatina and others. The hæmoglobinuria which is a recognized, although rare complication of various infectious diseases, may be referable to intoxication with unusually powerful parasitic hæmolysins, or to an exceptional lack of resistance of red corpuscles. Hæmoglobin, however, is not necessarily present in solution in the blood-plasma, for the destruction of the damaged red corpuscles may take place within the large phagocytes of the spleen and the hæmo-lymph glands, as is well known to occur on an extensive scale in typhoid fever and some other infections. A familiar example of the action of bacterial hæmolysins is the post-mortem reddening of the inner lining of the heart and blood vessels, an effect which may be due to putrefactive bacteria or may appear very soon after death, especially from septicæmia caused by *Streptococcus pyogenes*, which, as has been shown, may lake the blood during life.

The fact that certain common saprophytic bacteria may produce energetic hæmolysins, as pointed out by Kraus and Clairmont and by Todd, has a possible bearing upon the etiology of certain obscure anæmias not of infectious origin, particularly upon the interesting observations and the theory of William Hunter concerning their causation by absorption of toxins from the alimentary tract. Todd found cultures of *Bacillus megatherium* so strongly hæmolytic that the intravenous injection of 1 cc. of the filtrate into guinea-pigs was followed by hæmoglobinuria, 10 cc. being fatal. Human red corpuscles are sensitive to this hæmolysin.

Normal human and other blood-sera contain in varying amounts anti-hæmolysins, which protect the red corpuscles from the action of some of the bacterial hæmolytic agents. Specific anti-hæmolysins are readily produced by immunizing injections of bacterial hæmolysins and are generated also in the course of infections. Lang suggests that the augmentation of the osmotic resistance of the erythrocytes which has been noted in some infectious diseases, as well as in icterus and some other morbid conditions, may be a reactive phenomenon caused by the presence of hæmolytic toxins.

Intimately associated with the hæmolysins in cultures are the bacterial hæmagglutinins (Kraus and Ludwig),[20] substances which have the power to clump red blood corpuscles. Among unicellular organisms both the capacity to produce agglutinins and the aptitude for agglutination seem to be

[18] Besredka: Annales de l'Institut Pasteur, 1901, XV, p. 880.
[19] Kraus and Ludwig: Wiener. klin. Wochenschr., 1902, p. 382.
[20] Kraus and Ludwig: Wiener. klin. Wochenschr., 1902, p. 120.

very widely distributed. The bacterial hæmagglutinins, in analogy with the bacterial hæmolysins, are apparently of simpler constitution than the serum agglutinins, being destroyed at 58° C., whereas the latter are not injured by temperatures under 70° C. In order to demonstrate in cultures the hæmagglutinins it is generally necessary to eliminate in some way the action of the associated hæmolysins, which can be done by using small quantities of the culture fluid or by keeping the mixture of fluid and red corpuscles at zero temperature.

I know of no observations directly demonstrative of the action of bacterial hæmagglutinins within the living body in infections, but this subject is of such recent knowledge that it has been as yet scarcely investigated. Certainly there are morbid conditions which seem highly indicative of the operation of substances agglutinative of red corpuscles. Probably everyone with large experience in the examination of fresh blood in disease has noticed that sometimes red corpuscles, examined immediately after withdrawal of the blood, have a peculiar tendency to form clumps which cannot readily be broken up. This phenomenon, which is certainly suggestive of the action of an agglutinating agent, I have observed especially in some cases of septic infections and of cirrhosis of the liver.

Furthermore I would emphasize the support given by the recognition of hæmagglutinins to views advocated many years ago by Hueter and by Klebs concerning the occurrence of thrombi composed of coalesced red blood corpuscles. Such thrombi I believe to be not uncommon in typhoid fever and other infections, especially in small blood-vessels. I have elsewhere called attention to the evidence in favor of the interpretation of many of the hyaline thrombi as derived from agglutinated red corpuscles.

It can scarcely be doubted that substances agglutinative of white blood corpuscles are also produced by certain bacteria and that these are concerned in the clumping of pus cells and of leukocytes within the living body, but it would not be profitable to discuss this matter without more exact information than we now possess.

In this connection I may say that not only the discovery of the bacterial hæmagglutinins but also that of the hæmolysins and the leukolysins is likely to shed new light upon certain aspects of the difficult subject of thrombosis. The red corpuscles undergo various morphological changes under the influence of different bacterial hæmolysins acting with varying intensity. Distortions of shape, throwing out of projections, and detachment of colorless particles resembling platelets can sometimes be seen. These observations are of especial interest with reference to the doctrine, already strongly supported, that platelet thrombi originate from disintegrated red corpuscles. Levaditi, and Neisser and Wechsberg have described, as the result of intravenous injections of *Staphylococcus aureus*, areas of coagulative necrosis in the rabbit's kidney, which they attribute to thrombi composed of disintegrated leukocytes caused by the staphylococcus leukocidin, to which I have already referred.

I have dwelt at some length, although of necessity incompletely, upon the bacterial hæmolysins, leukocidins and hæmagglutinins, because we are better informed about these agents than concerning other members of this recently recognized class of bacterial toxins. I have already expressed the opinion that similar poisons acting specifically upon other cells of the body are produced by bacteria; indeed neurotoxins and nephrotoxins of this type have been reported. The difficulties in the way of direct proof of the existence of these other bacterial cytotoxins are greater than in the case of those acting upon the red and the white blood corpuscles, but doubtless they can be overcome. Of course we have evidence of the action of bacterial poisons upon various body cells, but this is not enough. At present we can apply only in a vague and unsatisfactory way to the explanation of pathological processes most of the knowledge of this kind which we possess. What is urgently needed is a separation of these poisons and a determination of their source, constitution, mode of action, and degree of specificity along such lines as have been followed so fruitfully in the investigation of the soluble diphtheria and tetanus toxins, those other toxins of bacteria and of venom already considered, and the cytotoxins of normal and of immune serum. The path leading apparently in the right direction has already been opened and, if I mistake not, its further pursuit is most promising of valuable results in the near future.

Consider by way of illustration how helpless we now are in our efforts to explain the characteristic lesions of typhoid fever on the basis of our knowledge of the properties of the typhoid bacillus. That these lesions are referable to the action of toxins cannot, I think, be seriously questioned. Especially from the investigations of Mallory we know that the most characteristic histological changes of this disease consist in the proliferation of the reticular or so-called endothelial cells of the lymphatic tissue of the intestine and the mesenteric glands and of similar cells in the splenic pulp, and in the assumption by these proliferated cells of remarkable phagocytic activities toward the lymphocytes in the former situations and toward the red corpuscles in the spleen. Mallory believes that these changes are best interpreted by supposing that the typhoid toxin directly stimulates to proliferation the endothelial cells, which then devour their offspring, the lymphocytes, and the red corpuscles. I have suggested as another explanation that the typhoid bacillus produces a lymphocytotoxin and an hæmolysin, and that the proliferation of the fixed cells is partly compensatory and partly for the increased production of macrophages. We already know that this bacillus generates a hæmolytic agent, and we also know that one of the effects of injection of hæmolysins is to increase greatly the number of macrophages containing red corpuscles in the spleen.

Through the kindness of Professor Flexner I have had the opportunity of studying the extraordinary changes produced

in all the lymphatic glands and in the bone marrow of rabbits by injections of lymphotoxic or myelotoxic serum obtained by treating a goose with lymphatic or marrow tissue of the rabbit. One of the most striking effects of this poison for lymphocytes and other leukocytes is the very extensive proliferation of the reticulum cells in the lymphatic nodes and of the marrow cells. In the light of these observations it is clear that a positive demonstration of the production of a lymphotoxin by the typhoid bacillus would materially advance our understanding of the morbid anatomy of typhoid fever.

Another lesion of this disease only second in importance to those mentioned is the occurrence of plugging of the small vessels. Dr. Fisher in my laboratory has recently shown that such thromboses are produced by the experimental inoculation of rabbits with the typhoid bacillus. I have already pointed out that many of these plugs are agglutinative thrombi.

Of course infectious diseases other than typhoid fever could also be cited, did time permit, as equally forcible illustrations of the aid which pathology may reasonably expect from more precise knowledge of the bacterial cellular poisons. It is probable that such knowledge will lead to improvements in the quality for therapeutical purposes of the so-called bacteriolytic sera, some of which, as now prepared, are not so wholly devoid of antitoxic properties as is often represented. We may also anticipate from investigations of the character indicated much light upon one of the most puzzling of bacteriological problems, the localization of bacteria in disease. Toxic lesions and the plugging of small blood-vessels are certainly often of decisive influence in determining this localization, as has been demonstrated especially for the staphylococcus pyæmias by Muscatello and Ottaviano.[21]

The toxins to which I have chiefly directed your attention in this lecture are those produced by bacteria. But, as already pointed out, we now know that the animal body has the power to produce specific poisons directed not only against invading bacterial cells but also against all sorts of foreign cells. Following the discovery by Belfanti and Carbone in 1898 of this capacity in relation to injections of blood a wholly new domain of biology has been opened to experimental research. Attention has been withdrawn for the moment to a considerable extent from the bacterial toxins and concentrated upon the animal cytotoxins. Here new facts and conceptions of absorbing interest have been disclosed in an abundance and with a rapidity which are simply bewildering.

It was my original design to include in this lecture a consideration in some detail of these animal cytotoxins but so much time has been occupied with other aspects of the subject that I am compelled to abandon this intention. This is perhaps less to be regretted inasmuch as I understand the main purpose of these lectures to be the presentation of applications to medicine and surgery of scientific discovery, and it is precisely this side of the recent work on animal cytotoxins which seems to me in the main not yet ripe for profitable discussion on this occasion. It is true that facts of much scientific and practical interest have been discovered by the investigations, initiated by Shattock and by Grünbaum, followed by Landsteiner, Ascoli, Eisenberg, Kraus and Ludwig, and others concerning the isoagglutinative and isolytic properties of human sera in health and in disease. But the really great practical questions in this domain relate to the production of autocytotoxins in the human and the animal body. What is the nature of that very efficient regulatory mechanism underlying the horror autotoxicus (Ehrlich) which prevents either the action or the formation of autocytotoxins in consequence of absorption of our own degenerated and dead cells? Can this protective mechanism be overthrown by pathological states and self-generated cellular poisons become operative in the causation of anæmias, hæmoglobinurias, chronic interstitial inflammations, uræmia, eclampsia, epilepsy, and other diseases? To these and similar important questions the existing experimental data seem to me too insufficient and inconclusive to furnish any decisive answer at present. I share, however, the hope and belief of many that here is a field for exploration which, although surrounded with many difficulties, gives promise of discoveries of a far-reaching and important nature. I anticipate that some future Huxley lecturer will find in this realm a fascinating theme.

In this connection may be mentioned the great pathological interest pertaining to the recent investigations of Jacoby, Conradi and others on the phenomena of self-digestion or autolysis of inflammatory exudates and necrotic material within the living body. One can readily convince himself of the energetic action of autolytic ferments by the simple experiment of placing a piece of fresh pneumonic lung in the stage of gray hepatization under chloroform and noting the rapid solution of the exudate, in contrast with the absence of this process in earlier stages of the disease. Conradi finds that bactericidal substances, to which he attaches much importance, are produced in tissues and cellular exudates undergoing autolysis.

Although my theme relates especially to the bearing of studies of immunity on pathology, it is hardly necessary to say that these studies were primarily undertaken to elucidate the great problems of predisposition and of resistance to disease and that in this field they have borne their richest fruits. It is especially gratifying to note the close convergence of the two doctrines of immunity, the cellular and the humoral, brought about by these recent discoveries. On the one hand the phagocytic school, represented so brilliantly by Metchnikoff and his co-workers in the Pasteur Institute, recognize and apply to the fullest extent in the explanation of acquired immunity the cytolytic principles based upon the cooperative action of intermediary bodies and complements. On the other hand the humoral school,

[21] Muscatello and Ottaviano: Virchow's Archiv, 1901, CLXVI, p. 212.

led by our German confrères, which has been so fruitful in results of the greatest scientific and practical value, recognize the cells as the immediate source of the protective substances. There are many differences in details, especially in terminology and in interpretation, which make the divergence seem greater than it really is. The essential difference between the two schools concerns the place where the two forces, intermediary body and complement, unite. All are agreed that the intermediary body exists free in the blood-plasma, but Metchnikoff strenuously insists, especially on the basis of Gengou's experiments, that the complement or cytase is within the leucocytes, from which it is not secreted but can be liberated only through damage to these cells. This question certainly needs further investigation before it can be regarded as settled. The recent recognition of endocomplements through researches made in Ehrlich's laboratory marks a still closer approximation of the two schools.

The deeper insight which we have recently gained into the nature of the forces concerned in immunity makes especially desirable the systematic study of the blood and other fluids of human beings in health and in disease with reference to their content of specific anti-bodies, particularly of the bactericidal substances. It can scarcely be doubted that knowledge of this kind will be in various ways of practical value to the physician and surgeon. The simplest procedure and the one hitherto generally adopted is the estimation of the bactericidal power of the blood-serum in toto. For this purpose Professor Wright [22] has devised an ingenious method, which in his hands has furnished extremely interesting information concerning variations in the bactericidal power of the blood as regards the typhoid bacillus in health, under the influence of fatigue, in the course of typhoid fever and after anti-typhoid inoculations. The older methods, however, while not without value, do not inform us of the total content of the blood in immunizing substances, and have led to very discordant results, particularly as to the influence of infection upon the bactericidal power. Thus Conradi [23] finds, in opposition to most previous experimenters as well as to the later results of Wilde, that infection with the anthrax bacillus does not at any stage influence materially the bactericidal properties of the blood.

A useful and readily applicable method for the determination separately of the intermediary bodies and of the complements of human serum is urgently needed. When one takes into consideration the plurality of complements and of intermediary bodies, the fallacies of interpretation which may arise from failure to take account of anti-complements, of anti-immune bodies, of complementoids, of amboceptoids, of deviation (Ablenkung) of complements, and other principles in this complicated subject it is clear that the problem is not an easy one.

Notwithstanding these difficulties work has already begun along these new lines and has led to interesting results. We know that the content of the blood in specific anti-bodies, and especially in complements, varies in significant ways under diverse conditions, as in infancy and in adult life, in health, in different states of nutrition, under the influence of fatigue, of inanition, of pain, of interference with respiration, of alcohol, and in disease. The infant comes into the world with protective anti-bodies in its blood smaller in amount and less energetic than those possessed by the healthy adult. It is an important function of the mother to transfer to the suckling through her milk immunizing bodies, and the infant's stomach has the capacity, which is afterward lost, of absorbing these substances in an active state. The relative richness of the suckling's blood in protective anti-bodies, as contrasted with the artificially fed infant, explains the greater freedom of the former from infectious diseases.

The important question of the influence of pre-existent disease in predisposing to infection has been brought nearer to a solution by recent studies of immunity. Schütze and Scheller [24] have demonstrated that while the normal rabbit promptly regenerates the complements used up in consequence of the injection of hæmolytic serum, a rabbit infected with the hog-cholera bacillus has lost this capacity. My former pupil, Dr. Longcope, has kindly placed at my disposal the unpublished results of an investigation which he is making under Professor Flexner's direction at the Pennsylvania Hospital of the intermediary bodies and the complements in human blood in different diseases. Colon and typhoid bacilli are used as the tests, as, unless one accepts Bordet's doctrine of the unity of complements, it is more important for the study of problems of infection to determine bacteriolytic rather than hæmolytic anti-bodies. One of the earliest results of the systematic bacteriological examinations which we make at all autopsies at the Johns Hopkins Hospital was the recognition of the great frequency of terminal infections, formerly often undetected by the clinician, in chronic diseases, particularly of the heart, the blood-vessels, and the kidneys.[25] Dr. Longcope finds, although not regularly, still in many cases of these diseases a marked reduction in the quantity of complements, which may amount to a total loss of the colon complements. The analysis of the cases brings out unmistakably a definite relation between this loss of complement and the predisposition to infections.

The study of a series of acute infections, chiefly of a surgical nature, shows that in the course of the infection complements are being constantly used up and regenerated,

[22] A. E. Wright: Lancet, 1898, I, p. 95; 1900, II, p. 1556; 1901, I, pp. 609 and 1532; and 1901, II, p. 715.

[23] Conradi: Zeitschrift für Hygiene, 1900, XXXIV, p. 185; 1901, XXXVIII, p. 411.

[24] Schütze and Scheller: Zeitschr. f. Hygiene, 1901, XXXVI, pp. 270 and 459.

[25] Flexner. A statistical and experimental study of terminal infections. Journal of Experimental Medicine, 1896, Vol. I, p. 559.

and that at any given time there may be an excess or a reduction of the bactericidal power of the blood. Thus far it has been found impossible in these acute infections to attach any prognostic significance to the amount of complement or of bactericidal power. Hyperleucocytosis was often, although not invariably, associated with high content of complements for the bacteria tested.

Although we have traversed, gentlemen, in this lecture a path which I fear has seemed to you a long and winding one, I am conscious that I have been able to point out the features of the prospect only imperfectly and incompletely. The extent and the richness in details have been embarrassing. I trust, however, that I have been able to indicate in some measure the great interest and importance to biology, to physiology, to pathology, to every department of medical science and art of investigations which have led to a deeper insight into certain manifestations of cellular life. What has been conquered by these investigations is simply a bit of new territory pertaining to the intimate life of the cells, and we find here, as whenever we are able to penetrate deeper into this life, that there comes a flood of new light into every department of biology. The researches on immunity, which to some of short vision once seemed to threaten the foundations of cellular pathology, have served only to strengthen them. These researches, which have already led to the saving of thousands of human lives and will lead to the saving of untold thousands more, have been carried on by the experimental method and can be conducted in no other way. This method is as essential for the advancement of medical science as for that of any of the natural or physical sciences. To restrict unnecessarily and unjustifiably its use is nothing short of a crime against humanity. It is an evidence of the robust vitality of English physiology and medicine that in spite of unwarrantable obstacles thrown in their path their contributions to science in recent years have been so numerous and so important. The influence of English thought and action is great with us in America. See to it, my colleagues and men of science in these British Isles, that you retain for yourselves and hand down to your successors, at least without further impairment, the means of promoting medical knowledge and thus of benefiting mankind.

THE IMPORTANCE OF A MORE RADICAL OPERATION IN CARCINOMA CERVICIS UTERI AS SUGGESTED BY PATHOLOGICAL FINDINGS IN THE PARAMETRIUM.

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No wonder that the laity and even some physicians consider cancer of the cervix of the uterus an incurable disease, for three-fifths of the patients admitted to this hospital with cancer of the cervix come too late for anything but palliative treatment. Of 143 patients in which hysterectomy has been done, 21 cases have died as a result of the operation, giving a primary mortality of 14.6 per cent. Three years or more have elapsed since the operation in 69 cases which we have been able to follow, and at the end of that time 20 were living, but 6 of these later had recurrences, thus giving a percentage of recurrences after three years and more, of 79.7 per cent. When we consider those cases in which five years or longer have elapsed since operation we find that there have been 49 whom we have been able to follow, and of this number the growth returned in 43, or 87.7 per cent. We realize, however, that five years is not long enough, for 2 of our patients have died at the end of 6 and 7 years from general carcinosis without a return in the vaginal vault, and a third is living, with a small growth in the vaginal scar, five and a half years after operation, there having been symptoms referable to it for only two months.

The comparison of statistics is very unsatisfactory, for many will operate on favorable cases only and will include in their statistics those cases alone in which they think that the entire growth has been removed; while others (as has occurred in many instances in our operating room), have realized before the operation that the growth was probably ineradicable and at the close of the operation have felt sure that the entire growth had not been removed. Generally the unfavorable prognosis has been speedily confirmed; on the other hand, we have had the satisfaction of seeing a few cases which are apparently well two and three years after operation, but which were considered unfavorable even at the close of the operation. Wertheim has emphasized that the induration of the broad ligament may be inflammatory and not cancerous in origin, and as we know, enlarged lymph glands do not necessarily indicate carcinoma. It is consequently impossible to make a positive prognosis before an operation or even at the close of one. We have every reason to expect, and even promise, a much higher percentage of cures in the future, for great advances have been made in recent years in two directions:

First, not only the medical profession, but also the laity, realize the importance of making an *early* diagnosis.

Second, the operation is *more radical*, not only in advanced cases but also in *favorable ones.*

The importance of removing the lymph glands along the pelvic vessels has been emphasized by many operators and

credit is due especially to Wertheim,[1 2 3] who has reported 3 series of cases operated upon by his method. In 30 of the 90 cases reported by him, there was evidence of glandular metastases, as determined by serial sections of the glands. He advocates not only dissecting out the glands but also a wide excision of the parametrium and vagina. While he thinks it is better always to remove the glands, he has found carcinoma only in the enlarged glands, consequently he has removed them in only 22 of the 30 cases last reported by him, and in 11 of these cases carcinoma was found. He has shown that there is no relation between the size of the primary growth and the presence or extent of glandular involvement; *i. e.*, the local growth may be very small and yet there may be extensive glandular involvement. On the other hand, the primary growth may be large and there may be very few or no metastases to the lymphatic glands.

Doederlein [4] reports 26 cases operated upon by Wertheim's method. In 18 the glands were removed and in 7 of these carcinoma was found. In 1895 Ries,[5] Rumpf [6] and Clark [7] advocated that the lymph glands should be removed in hysterectomy for cancer of the uterus. Their operations are apparently similar. Ries,[8] in a paper read before the Illinois State Medical Society, May, 1901, emphasizes the importance of this procedure and calls attention to the necessity of serial sections in order to prove the existence of carcinoma in the glands, and that one cannot tell by palpation whether or not the gland contains carcinoma, for a large, firm gland may be normal and a small, soft one may contain metastases. Clark,[9] in an article which appeared, May, 1901, states, "As a result of my own study of glands which have been removed at the time of radical operation for cancer, I have gradually reached the conclusion that glandular metastases are much less frequent than I supposed when I originally described my own operation in 1895. Recently I have become more and more conservative as to my statements on this point, for the result of Cullen's very careful investigation of all cancer cases operated on in the Johns Hopkins Hospital proved that metastases are comparatively infrequent." He then considers the work of Wertheim, who emphasizes the importance of serial sections, and adds that "if this be true we may be wrong in assuming that metastases are not frequent." In speaking of the operation, he says, "Notwithstanding my conviction as to the necessity for the removal of the glands, I believe that the condition of the patient must be considered carefully before proceeding to this step. My rule is, therefore, to complete first the chief part of the operation, the removal of the uterus, and if then the patient's general condition justifies it, the iliac glands may be dissected out. Even then, I consider the removal of the glands of prognostic rather than curative value, for if they are involved as shown by microscopic examination, I do not believe the patient will escape a recurrence of the cancer." Wertheim, in the report of his last series of 30 cases, refers to patients who were operated upon 2, 2½ and 3 years ago, where cancerous glands were removed, and as yet there is no evidence of a recurrence. The results of the work in this hospital in regard to the involvement of the lymph glands is of little value when negative, for they have not been systematically removed and serial sections have been made in only a few instances.

Associated with these 143 cases of hysterectomy for cancer of the cervix in this hospital there have been 17 instances of unintentional injury to the ureter. The more radical the operation and the greater the endeavor to get well outside of the growth, the more liability there is to be an injury to the ureter. These injuries have been of various kinds, as clamping, ligating, and incising the ureter. Some were recognized during the operation and the ureter was released or repaired; in others, the injury was not discovered until afterwards. In 7 instances, post-operative uretero-vaginal fistula occurred from injuring the blood supply of the ureter. The main blood vessels of the ureter are in its outer loose fibrous coat. When the ureter is adherent to the growth, dissecting it free will injure these vessels, as will also clamping it; and the injury may be sufficient to give rise to a slough and a resulting urinary sinus. From our experience it would seem that when there is lateral extension of the disease sufficient to cause the ureter or ureters to become adherent, it is better to remove all the tissue between the growth and the pelvic wall, thus including the vesical portion of the ureter and implant the end of the ureter in the bladder. The points in favor of this procedure are that—

1. The growth is less likely to return.

2. Uretero-vaginal fistulæ are probably less likely to occur.

3. The time spent in doing it is probably no greater than would be required to dissect the ureter free.

In July of this year I had an opportunity to operate on a case of cancer of the cervix in which clinically there was some induration of the right broad ligament. I therefore planned to sacrifice the right ureter and implant it in the bladder. Previous to the operation I reviewed the operations of Clark, Wertheim and others, and at the same time worked out a form of uretero-vesical implantation, which I tried with success in dogs. From the above considerations and a study of the anatomy of the pelvis I developed the various steps of an operation which I first tried upon the cadaver. Since then three carcinomatous uteri have been removed by this operation—the first by myself and the remaining two by Dr. Schenck, Resident Gynecologist. Another was attempted but abandoned on account of the very wide extension of the disease and the difficulty in obtaining a satisfactory exposure, due to the depth of the pelvis and very thick abdominal walls; the uterus and only a portion of the growth were removed. The operation which I am about to describe is in general the one we used, modified by the experience gained from these cases. In the first case the lower end of the right ureter was excised and in the second the left, which was double, and in the third both ureters.

OPERATION.

1. A preliminary catheterization of the ureters, with silk bougies, before the patient takes the anesthetic. I failed in my case on account of the vesical irritability, but Dr. Schenck succeeded in his two cases and found them of great assistance.

2. After the patient is anesthetized she is placed in the perineal position and a long proctoscope is inserted through the rectum high up into the large intestine in order to get rid of any gas or fecal matter which may be present.

3. A row of interlocking catgut sutures is now placed around the vagina, 3 cm. below the growth. These sutures are passed with a large curved needle, include large masses of tissue, and extend laterally as far as the needle will permit, while a finger in the rectum prevents their being passed too deep posteriorly. After all these sutures have been passed they are tied. This procedure is for the purpose of occluding the large vaginal and paravaginal veins which give rise to the venous hemorrhage so troublesome and at times dangerous, when a wide lateral dissection of the growth is attempted from above. Dr. Miller, at one time resident gynecologist, introduced a very useful step in abdominal hysterectomy for cancer of the uterus. He placed sutures in the vaginal wall below the growth and with a Pacquelin cautery burned through the vaginal wall between the sutures and the growth. This was done preliminary to the abdominal operation and the groove caused by the cautery indicated how much of the vagina was to be removed, and the sutures were for the purpose of preventing bleeding from the vaginal wall. These sutures were passed with a small needle and probably only occluded veins in the vaginal wall. Profiting by his work, I go a step further, using as large a needle as the vagina will permit and passing the sutures as stated, but do not burn through the vagina, for the tying of these large masses of tissue constricts the vaginal canal so that the burning is not possible. The sutures should not be placed too near the cervix in the antero-lateral portion of the vagina, for there is danger of ligating the ureters, should the operator not wish to sacrifice them later.

4. A retention catheter is now placed in the bladder, so that the bladder may be filled with sterile fluid to help detect a hole in the bladder and also to aid in the ureterovesical implantation.

5. The patient is now placed in the Trendelenberg position and the abdomen is opened from symphysis to umbilicus. A self-retaining retractor is used. After packing back the intestines with gauze, the ovary of the side on which the ureter is to be resected is grasped by a pair of forceps and pulled downwards and outwards, thus making taut the ovarian vessels and peritoneum covering the iliac vessels. The peritoneum is now split below and parallel to the ovarian vessels as high up as the origin of the internal iliac artery. The ureter can be seen in a thin patient lying in the lower peritoneal flap, and its blood supply is not interfered with. Beginning at the origin of the internal iliac artery we now dissect downwards removing the fat and lymphatic structures, including glands from along the iliac vessels, thus exposing the branches and removing the tissue *en masse*. By using a blunt dissector and always dissecting down along the vessels, hemorrhage may be avoided. One should never dissect upwards for the following reasons:

(a) For then the instrument will enter the angle between the branches of the iliac vessels and may tear off one, and when a branch is torn in this manner from a larger one the hemorrhage comes from both vessels if they are veins, as they are very apt to be, or possibly from only the larger one, if it is an artery.

(b) By dissecting downwards the lymphatics and adipose tissue can be removed *en masse*.

(c) It is always much safer to work from a more dangerous to a less dangerous area, for when one works towards the large vessels, a slip of the instrument may give rise to serious hemorrhage.

After exposing the vessels in this manner down to the uterine artery, the ovarian vessels and round ligament are cut. The uterine artery is tied twice at its origin, taking care to include in the ligature the vaginal artery should it arise from the internal iliac, but not the superior vesical artery, and cut between the two ties. I do not think that there is anything to be gained by tying the anterior branch of the internal iliac, as was done in two of the cases, and there is the disadvantage that the blood supply of the pelvis may be injured.

6. The other side is treated in a similar manner, if both ureters are to be removed, as was done in one instance; if not, the exposure of the vessels is the same and the removal of the lymphatics may be the same and the uterine vessels are tied and cut at their origin, and then lifted up and dissected away from the ureter, taking care not to injure its outer vascular coat.

7. The uterus is now pulled upwards towards the umbilicus and the bladder is dissected free from the cervix and not the cervix from the bladder, for in the former, while there is greater danger of injuring the bladder, there is less danger of cutting into the diseased cervix. The dissection is carried on down to the ureters and, if thought best, one or both are cut off close to the bladder.

8. If the lower end of the ureter is to be sacrificed, it should be amputated just above the place where the uterine artery crosses it, and all the tissue lateral to the cervix including the lower portion of the excised ureter, may be dissected from the pelvic wall. If the lower end of the ureter is not to be sacrificed, the parametrium is dissected free mesial to the ureter.

9. The utero-sacral ligaments are next cut and the rectum is dissected from the cervix and vagina.

10. The dissection is now carried on around the growth on all sides and down the vagina to the preliminary catgut ligatures. The gaping openings of the large veins can be seen in these cases, some thrombosed and others empty, perfectly controlled by the preliminary catgut sutures. One

has to be careful not to go too far laterally below the growth, for here one may cut veins which come in from the sides and are not controlled by the preliminary sutures. Wertheim's clamps are now applied to the vagina and the vagina is cut below them and the tissue removed.

11. The uretero-vesical implantation.

The table is placed in the horizontal position. The ureter is split laterally for a distance of 8 mm., so as to form a dorsal and a ventral flap. A silk suture with a needle at both ends is passed through each flap from side to side just beneath the ureteral mucosa. The bladder may be filled with sterile water or else the posterior wall may be pulled from the anterior wall by thumb forceps. Choose a place in the bladder with a good blood supply, make two parallel horizontal incisions, the width of the ureter apart and as wide as the same and connect these two by a transverse incision. This gives a π incision, and on spreading the flaps apart forms a square hole in the bladder with two lateral flaps. The needles are next passed through this hole and through the bladder wall from within out, those from the dorsal flap, coming out below the opening about 5 mm. from the edge and the width of the ureter apart, and those from the ventral flap coming out at corresponding places above the opening. The ureter is now drawn into the bladder by the sutures and they are tied. The lateral bladder flaps are now sewed to the side of the ureter with fine silk sutures which pass through ureteral and bladder wall down to the mucosa. The anastomosis is complete, except for the buttressing of some of the tissue about it. Its advantage is its simplicity. There is little chance for ureteral stricture on account of the square hole in the bladder; the implantation is strong, silk being used, two sutures of which pass through the entire bladder wall and ureteral wall except the ureteral mucosa, while the other two sutures include the ureteral and vesical muscular coats. All sutures are tied outside of the bladder, and are not exposed in the cavity of the bladder so as to form the nucleus for a stone. Nevertheless one should always make a cystoscopic examination before the patient is discharged to make sure that this has not occurred. The ureter and raw areas are now covered with peritoneum, the pelvis is drained through the vagina, and the abdomen is closed. The technique of covering the raw areas caused by abdominal hysterectomy for cancer of the cervix with special reference to the support of the bladder has been very carefully worked out by Krönig.[6]

Such an operation at present takes from 2½ to 3 hours. The passing of the preliminary sutures in the vagina takes from ten to fifteen minutes, while the abdominal operation, including the uretero-vesical anastomosis, takes from 2 to 2¾ hours. The uretero-vesical implantation can be done in ten minutes.

The advantages gained by sacrificing both ureters and removing the lymphatics along the pelvic vessels are well shown in Fig. 1, where all the tissue from pelvic wall to pelvic wall including the lower 4.5 cm. of the ureters was removed with the uterus and lymphatics along the pelvic vessels. One by drawing an imaginary line between the ureters and the cervix can see the difference between removing all this tissue and simply doing a "hysterectomy" for cancer of the uterus. The comparison between the two operations is also shown in Fig. 2, which is a cross section of a case where the ureter was sacrificed on one side only.

These three operations gave excellent opportunity to study the conditions found in the parametrium between the cervix and the pelvic wall, including the ureter.

I give a brief summary of the points of interest in these cases:

Case No. I. Gyn. No. 9802. Path. No. 6019.

Clinically the right parametrium seemed a little thicker than the left. Many sections were cut of this tissue; a few small lymph nodes, .5 to 1 mm. in diameter, were found along the blood vessels out as far as the ureter. Small groups of carcinoma cells were found in the lymph channels one-third of the distance from the cervix to the ureter. Somewhat similar conditions have been described by Cullen[11] and others. There was nothing in the section to account for the apparent increased density of the tissue. Had a vaginal hysterectomy been done, cancer would probably have been left behind.

There was no evidence of cancer found in the one lymph gland removed from the iliac vessels.

Case No. II. Gyn. No. 9860. Path. No. 6074 (Figs. 2 and 3).

Clinically the left parametrium seemed thicker than the right.

Blocks were cut from the parametrium and serial sections were made. At the level of the uterine artery, scattered along it and some of the other vessels were found lymph nodes from 1 to 3 mm. in diameter. These may have accounted for the apparent increased density of the tissue. There was not any evidence of cancer in the lymph nodes at this level. In a block taken at a lower level a few small lymph nodes were found along the veins. The diameter of the largest was 1.5 mm. and the largest number found in any one section was 5 (see Fig. 3), while many sections contained only 1 or 2, and some sections none. Cancer metastases were found in these small nodes, and Fig. 3 was drawn from a section in which cancer was present in the node marked *d*, which is lateral and posterior to the double ureter. In other sections cancer was found in a node at about the same position as the nodes marked *c*. These were the only nodes found in the parametrium with cancer and they would not have been found unless serial sections had been made, for many sections may be made of one small node 1 mm. in diameter, and only 1 or 2 of these sections will show cancer. Cancer was not found in the lymph spaces as in No. 1. The lymph glands along the pelvic vessels on the left side were not removed, for they could not be palpated. On the other hand, an enlarged gland lateral to the right ureter showed carcinoma, and yet the right parametrium felt normal and consequently the right ureter was not sacrificed. Had the ureter been sacrificed, we would have had an opportunity to

study this tissue between the cervix and pelvic wall, and possibly we may have found these small lymph nodes with cancerous metastases, for certainly a few scattered lymph nodes 1 to 1.5 mm. in diameter cannot be felt in a mass of fibrous and adipose tissue.

Case No. III. Gyn. No. 9903. Path. No. 6103 (Fig. 1).

Clinically both ureters were adherent to or surrounded by the thickened parametrium. The growth had extended out to the ureters and it would have been impossible to remove the uterus and leave the ureters without injuring them and leaving the malignant growth behind, so it seemed that the lower ends of both ureters must be sacrificed or the operation abandoned. Therefore the lower ends of both ureters were removed with the uterus by Dr. Schenck.

In vaginal and likewise abdominal hysterectomies the separation of the uterus from the surrounding tissue takes place mesial to the ureter in tissue composed of fibrous and adipose tissue, blood vessels and lymphatics. We may very well speak of it as the axilla of the cervix. The cervix is hard and firm, this tissue is loose and easily torn, therefore the line of separation will naturally take place at the junction of the hard tissue and the loose, very near the cervix. Should there be any lateral extension of the disease into the lymphatics it will probably be left behind.

If it is an abdominal operation and the operator removes the enlarged lymph glands, the procedure seems to me to be analogous to that of a surgeon who excises a cancer of the breast, dissects out some enlarged lymph glands in the neck and leaves untouched the lymphatics in the axilla. Wertheim emphasizes the importance of a wide excision of the parametrium and vagina and a dissection of the pelvic lymph glands. He exposes the ureter and ties the uterine vessels just over it. The uterus is then removed with a wide excision of the parametrium and vagina. The lymphatics are now dissected from the pelvic vessels if the glands are enlarged; otherwise they are not removed. Can he by such an operation remove all the tissue from the cervix to the pelvic wall without interfering with the blood supply of the ureter or leaving cancer in the pelvis? Would such an operation remove a lymph nodule posterior and lateral to the ureter, as *d* in Fig. 3?

In regard to vaginal hysterectomy, it is impossible to remove lymphatic glands and we realize that they are involved in at least one-third of the operable cases, as shown by Wertheim. But then, he who advocates vaginal hysterectomy may say that when the lymphatics are involved the case is hopeless. This must be proven.

CONCLUSIONS.

1. Carcinoma of the cervix may metastasize to small lymph nodes along the blood vessels, and these nodes may have a diameter of not over 1 to 1.5 mm.

2. As the nodes are very small it may be impossible to feel them either in the parametrium or along the pelvic vessels.

3. These metastases may be so minute and scattered that they can be discovered only accidentally or by cutting serial sections.

4. In every case of hysterectomy for carcinoma of the cervix the lymphatics along the pelvic vessels, and also the parametrium, should be removed *en masse* with the uterus, because an enlarged gland is not necessarily an invaded gland and cancer may be present in very small lymph nodes which can not be palpated; therefore clinically it is impossible always to diagnose cancerous lymphatics.

5. Should the ureter be adherent to the parametrium, the lower portion of it should be sacrificed and all the tissue from cervix to pelvic wall removed, for if the ureter is dissected free, two things are very apt to occur: (1) The disease will probably return. (2) An uretero-vaginal fistula will probably occur from injury to the blood supply of the ureter.

6. To the above should be added a last suggestion that in every case of hysterectomy for cancer of the cervix the lymphatics should be removed from the pelvic vessels from above downwards, together with the uterus and all the tissues lateral to the cervix from pelvic wall to pelvic wall undisturbed, including the lower 4 cm. of the ureters; and the ureters should be implanted in the bladder.

Wertheim has shown that the local disease may be very small, and yet the glands may be involved, and if the glands are involved probably the tissue between them and the cervix is also involved and the involvement may be in such small areas that it cannot be diagnosed clinically. So one would think that probably the *most radical operation* was indicated in the *most favorable cases* as much if not *more* than in the cases with extensive involvement, for in the former there is the greater chance of removing the entire growth.

These questions naturally arise: Is such an operation justifiable? What will the primary mortality be? What will be the percentage of cures? Is it necessary to sacrifice the lower end of the ureter, and why can it not be dissected free and the tissue all about it removed?

These answers all require time and work, and so far neither sufficient time has elapsed nor enough work has been done to confirm or condemn such a procedure. As stated, the operation with removal of one ureter has been done twice, with one death. In that instance the posterior iliac veins and rectum were accidentally injured and the patient died from shock with post-operative anuria. The complete operation with removal of the lower ends of both ureters has been done once, and that by Dr. Schenck, the ureters being adherent to the growth. In another case the operation was attempted, but abandoned on account of the wide extension of the disease and large size of the patient, making the exposure very difficult. What will be the ultimate fates of the two patients who are living remains to be seen.

In any operation there is the possibility of perfecting the various steps so that they may not only be done more quickly but also with less shock to the patient. A very good example of this is shown in the 90 cases reported by Wertheim. The duration of the operation in several cases in the first series reported by him was from 2 to 3 hours, the same

length of time that we have consumed in this operation, while in his last 30 cases the duration of the operation, including the closure of the abdomen, varied from 1 to 1½ hours, just one-half the time of the cases above referred to. In his first 30 cases there was a primary mortality of 12 cases; in the second 30, of 5; and in the last 30, only 3. And I am sure all physicians interested in cancer of the uterus are looking forward to find out what per cent of the cases surviving the operation are free from recurrence at the end of three and five years, and whether the recurrence is local or glandular, and especially what per cent of those in whom cancerous glands were removed are well at the end of these periods. For, as stated, Wertheim removes the uterus with as wide an excision of the parametrium as is possible without injuring the blood supply of the lower end of the ureter, as has been worked out by Feitel.[12] The lymphatics are then removed from about the pelvic vessels. One would think that if the lymphatics about the pelvic vessels are cancerous, probably the tissue between them and the growth would also contain cancer, hence we could expect a return in these cases in the tissue about the ureter and lateral to it near the pelvic wall, which would have been removed had the lower end of the ureter been sacrificed as has been described.

The operation which I have described is more difficult than the one described by Wertheim, so we must expect that it will take longer, and we can hardly hope ever to be able to do it in 1 and 1½ hours, as Wertheim is able to do. Likewise, the operation will undoubtedly be attended with a higher primary mortality on account of the greater length of time consumed in doing it, the greater liability of post-operative infection due to the large cavity left in the pelvis by the removal of so much tissue, which fills in very slowly, and also to complications which may be associated with the uretero-vesical implantation. The hemorrhage from the vaginal and paravaginal veins, so dangerous in our previous operations, can apparently be controlled by preliminary vaginal sutures, and thus one great source of shock avoided.

All the steps in the operation are open to development and much improvement. I am sure that many of us who are only too well acquainted with the mental and physical torture, the pain, the vesical and rectal fistulæ, etc., so generally associated with the clinical course of cancer of the cervix not operated upon, and the fact that such a large per cent recur after operation, which means that they have not escaped the above mentioned misery, will agree that any operation, no matter how severe, which gives the highest percentage of cures is the one to be developed, not only in the advanced cases, but *especially in the early* ones, for, as stated, in the latter there is the greater chance for a cure. And such an operation is the removal of the primary growth with as wide an excision as possible, and *en masse* with it, the tissue *undisturbed*, containing the lymphatics draining the region of the growth. We all know what such an operation has done for cancer of the breast and also for cancer in other portions of the body, and cancer of the cervix of the uterus is not an exception.

In closing, I wish to thank Dr. Kelly for permission to make this report and Mr. Max Broedel for assisting me in making the illustrations.

October 6, 1902.

Additional Remarks.

The difficulty of obtaining a satisfactory exposure in fleshy individuals, as well as the long time spent working in the peritoneal cavity, a great factor in the causation of shock, suggests the use of the retroperitoneal route. Through incisions lateral to the outer borders of each rectus or a curved cross abdominal incision, the peritoneum could be exposed and dissected free from the pelvic wall. Thus, the greater part of the operation could be done extraperitoneally; namely, the dissection of the lymphatics from the pelvic vessels, the control of the uterine artery, and freeing of the cervix and parametrium from the pelvic walls and bladder. The time spent working in the peritoneal cavity would be very little, thus diminishing both the shock of the operation and the chance for infection. Two methods of operating by the extraperitoneal route have already been described by Amann[13] and Mackenrodt.[14]

A feature of much interest in the development of a more radical operation is the possibility of saving the ureters in the cases where the parametrium is apparently not involved by the carcinoma. The blood supply of the ureter varies greatly; two of its main vessels are derived from the renal and ovarian arteries and all along its course it may receive branches from the vessels nearest to it, as the aorta, iliacs, uterine and vesical arteries. Monari[15] has called attention to the fact that the vessels run in the outer perimuscular connective coat, and emphasizes the importance of the branches from the renal and ovarian arteries, for they may accompany the ureter almost to the bladder. He states, therefore, that the ureter may be freed for nearly its entire length without causing a slough. This statement of Monari has been confirmed clinically, for many operators have isolated the ureter for a distance of several centimeters and yet a slough has not taken place. Wertheim had 5 cases of post-operative ureteral fistulæ in his second series of 30 cases, and 3 of the 5 were double, making in all 8 fistulæ. He had been isolating the ureter for nearly its entire pelvic length. Feitel studied the blood supply of the pelvic portion of the ureter and showed that the upper part received branches from the aorta and iliac vessels and that these branches entered the ureter from the mesial side, while those supplying the lower portion were derived from the uterine and superior vesical arteries, thus coming in lateral to the ureter. As a result of Feitel's work, the ureter in the next series of 30 cases was exposed differently. The peritoneum over the upper pelvic portion of the ureter was split open lateral to it and then the incision crossed the ureter and was continued down mesial to it, and thus the blood supply was not interfered with. In this series of 30 cases there were only 2 ureteral fistulæ and they resulted

from dissecting free the ureters, which were adherent to the growth, thus injuring the perimuscular vascular coat. We can see that there is clinical evidence for believing that in some cases the renal and ovarian vessels are sufficient to supply the ureter for nearly its entire length. On the other hand, there is equally strong evidence to show that in other cases the blood supply from the pelvic vessels is apparently necessary for the nourishment of the lower portion of the ureter. If the lower end of the ureters is not sacrificed, we realize that the tissue containing the lymphatics which drain the cervix has not been removed undisturbed, also that possibly carcinomatous tissue has been left behind; and then again that the blood supply of the ureter may have been injured sufficiently to give rise to a fistula, due either to handling of the ureter, thus injuring its perimuscular vascular coat, or injuring directly the blood vessels supplying that portion of the ureter. After the exposure of the ureter, whether its outer perimuscular vascular sheath is injured or not, it should again be brought in contact with tissue upon which it usually rests and should be covered with peritoneum. A drain should extend to a place near the ureter but should never come in contact with it. Monari has shown that the ureter of a dog may be dissected from its outer vascular sheath for a distance of 12 or 13 cm., and if the operation is done carefully and it is placed back in the sheath and the above directions are followed, a fistula will not result; but when a drain separates a portion of the ureter from its sheath a fistula occurs.

The importance of the above has been emphasized by other writers. Undoubtedly many post-operative fistulæ would not have resulted had these precautions been taken.

LIGATION OF ONE URETER AS AN AID IN THE MORE EXTENSIVE OPERATIONS FOR CARCINOMA OF THE CERVIX.

Landau,[16] in a combined abdominal and vaginal hysterectomy for carcinoma of the cervix, found it necessary to resect the lower 5 cm. of the right ureter, which was surrounded by carcinoma. On account of the length of the operation and the difficulties of an uretero-vesical implantation, due to the amount of the ureter resected, he tied the renal end of the ureter and dropped it, intending later to remove the kidney. The case was later more fully described by Weinreb.[17] The patient was seen six months later, apparently in the best of health, without any evidence of a return of the growth or of the formation of a tumor mass in the kidney region. Landau, on account of the favorable results of this case and of the cases of ligation of the ureter for surgical injuries to that organ reported by Bastianelli,[18] Futh [19] and Phaenemenow,[20] suggests that this procedure may enable one to remove carcinomatous uteri which would otherwise be considered inoperable.

I have been able to find in the literature but one other instance of intentionally tying the ureter in order to excise the lower end of it in a hysterectomy for cancer of the cervix, that by Bardenheuer.[21] The patient recovered from the operation, but died eight weeks later from renal infection.

There are many instances of unintentional ligation of the ureter during hysterectomy for carcinoma, especially by the vaginal route. We have been able to diagnose but one such case, Gyn. No. 1134, in this hospital, and the diagnosis was made at autopsy, the patient dying on the fourth day. One cannot say how much the injury to the ureter had to do with the death of the patient. Such an injury is suggested after operation when pain in the kidney region and along the course of the ureter arises and there is known to be a possibility of such an injury. These symptoms are made even more definite when in addition renal infection occurs or insufficiency of the other organ exists. A cystoscopic examination and catheterization of the ureters will aid in the diagnosis. Stoeckel [22] has called attention to the great difficulty in the diagnosis of such injuries. For in the absence of infection there are often apparently no definite symptoms, or such as there are may be easily obscured by the symptoms following such an operation. The other kidney, if sound, can readily adjust itself to the additional work and prevent the threatened uræmia. Stoeckel claims that the fistula which may result, as a rule makes evident the diagnosis of the injury and not the symptoms resulting from the occlusion of the ureter. The unintentional ligation of the ureter may at times be diagnosed from definite renal symptoms; at other times from the formation of a fistula; and then again, discovered at autopsy. Nevertheless, it would seem that there must be many instances where the ureter has been accidentally tied and the patient has recovered and the convalescence was considered uneventful.

There are three contraindications to this procedure in any operation:

1. When an uretero-ureteral or an uretero-vesical implantation is possible.

2. When pyuria is present or the ligation takes place in the presence of infection.

3. When renal insufficiency exists.

In two successful uretero-vesical anastomoses referred to in this paper, 4-5 cm. of the ureter were sacrificed and the implantation was easily accomplished under very little tension, and yet the bladder was not dissected free, as has been done by Kelly,[23] or the kidney pulled down, as suggested by Bovee.[24] Kelly claims that by freeing the bladder and drawing it back toward the posterior part of the pelvis to meet the shortened ureter, a distance of from 3 to 5 cm. can be gained. So it would seem to me that it would be possible to implant the ureter into the bladder in nearly every case in which it was possible to remove the growth.

One must realize that the ligation of the ureter in hysterectomy for cancer is not done under strictly aseptic conditions. Therefore, there is the additional risk of renal infection or the formation of a ureteral fistula, or both. In cases where the ureter has been involved by the growth there must be considered the possibility of the infection of the tissue about the ureter, the ureter itself, or even the pelvis of the kidney, from organisms present in the necrotic cancerous tissue. Also, abdominal hysterectomy for cancer of the cervix is

accomplished under more or less danger of infection of the pelvis, although the use of the Wertheim clamps has greatly lessened this. The sufficiency of the other kidney must be considered in all operations where one kidney is sacrificed, whether it is done by nephrectomy or atrophy caused by the application of a ligature to the ureter.

The question arises when the ureter is injured in this or any other operation where an uretero-ureteral or ureterovesical implantation is impossible, what should be done. If pyuria is present, the suturing of a ureter into a skin incision is probably the safest procedure. A nephrectomy may be done later if necessary. The anastomosis of one ureter into the other at present seems too difficult, and the results are too uncertain. The implantation of the ureter into the intestines is accompanied with too great a risk of renal infection. The substitution of a piece of the intestines to meet the deficiency, as suggested by Barbat,[25] is accompanied with less danger of renal infection. The implantation of the ureter in the skin incision as near the bladder as possible, with the view of later dissecting the bladder free to meet it, or the formation of a channel from a flap of the bladder wall to meet the deficiency, as described by Van Hook[26] and Boari,[27] offers valuable suggestions. The ligation of the ureter is apparently justifiable when necessary, but the ligated end *must* be placed beneath the skin so that any postoperative complications may be controlled. Should renal insufficiency manifest itself, then the ligature may be freed and the function of that kidney probably restored. In this respect the ligation of the ureter is preferable to nephrectomy. Should pyonephrosis occur one would have a means of relieving the condition. Of great importance should a leakage take place, due either to the slipping of the ligature or to necrosis of the ureter brought about by the ligature, then it could easily be recognized and an avenue for the escape of the urine formed. Fraenkel,[28] as the result of his clinical observation and animal experimentation, has urged the importance of this procedure.

I wish to take this opportunity to refer to a recent article of mine, "Ligation and Clamping the Ureter as Complications of Surgical Operations."[29] The effect of *complete* and *permanent* ligation of one ureter in animals, and the results in some of the instances where it has been done in man, as well as the finding of such injuries at autopsy, caused me to think that in the absence of *infection* and renal *insufficiency* such a procedure would usually give rise to little or no pain and would probably not be accompanied by any untoward symptoms. Therefore, I made certain statements, to this effect, which, although they may be true, are not justifiable in the present state of our knowledge of the subject. They were these:

"When only one ureter is occluded, the diagnosis is indeed very difficult, for in the majority of cases there are *no subjective symptoms.*" "It may be said that *generally* pain (renal or ureteral) is not present when the ureter is completely occluded"; also that "Complete and permanent occlusion of the ureter in the absence of infection leads to renal atrophy, etc." These conditions take place *usually* without any symptoms or evidence of constitutional disturbances, and probably without much shock."

One must remember, however, that the patient is unconscious for some time after the operation, and that the symptoms arising from such an injury could easily be obscured by those usually following such an operation, and also by the use of sedatives. In some of the cases reported the condition in the pelvis, which led to the injury of the ureter, may by compression have gradually caused a partial or complete atrophy of the kidney, as was considered in the cases reported by Bastianelli and Veit.[30] In such cases the ligation of the ureter would probably give rise to few or no symptoms.

Resection of the Ureters in Hysterectomy for Cancer of the Uterus where there has been Wide Lateral Extension of the Growth.

Hysterectomy for carcinoma of the cervix with resection of the lower end of the ureter and implantation of the ureter into the bladder when the vesical end of the ureter was found to be surrounded by the growth, has been accomplished with success by several operators. Penrose,[31] in July of 1893, was probably the first to do this in an abdominal hysterectomy. He employed a suture to draw the ureter into the bladder, a method suggested by the Van Hook[32] end-in-side uretero-ureteral anastomosis, from which the method described by me, as well as similar operations reported by others, have been developed. Schede,[33] in 1890, in a hysterectomy by the sacral route, resected a portion of the ureter and bladder wall which were involved by carcinoma and attempted to implant the ureter into the bladder, but failed. Westermarck,[34] in 1894, in a similar operation was successful.

Dr. Kelly[35] was probably the first, and, as far as I am able to learn, the only one, to resect the ureter and successfully implant it in the bladder by the vaginal route in a vaginal hysterectomy, March, 1899, Gyn. No. 6831. This case was erroneously reported as an abdominal hysterectomy and implantation. Previous to the ones referred to in this article, we have had in this hospital but one other instance of hysterectomy for carcinoma of the cervix with resection of the lower end of the involved ureter. This was done in January, 1900, by Dr. Kelly.[35] Gyn. No. 7510. During recent years other operators in this country and abroad have successfully resected the lower end of the ureter and implanted it in the bladder in hysterectomy for cancer of the uterus involving the ureter.

Chalot,[36] in 1896, advocated the preliminary ligation of both internal iliac arteries and the systematic transplantation of both ureters into the bladder if possible, otherwise into the rectum, in cases of cancer of the cervix of the uterus with wide extension of the growth. He reports a successful operation with implantation of the ureters into the rectum. One may find recorded, cases of the resection of ureters and their implantation into the bladder, as well as into the skin,

FIG. 1.—Gyn. No. 9903. Path. No. 6103. Natural size. In this instance the lymphatics were removed from the pelvic vessels from above downwards, together with the uterus, and undisturbed all the tissue lateral to the cervix from pelvic wall to pelvic wall, including the lower 4.5 cm. of the ureters; and the ureters were implanted in the bladder. By comparing this with the picture of the usual hysterectomy for cancer of the cervix, one can see what is gained by the more radical operation.

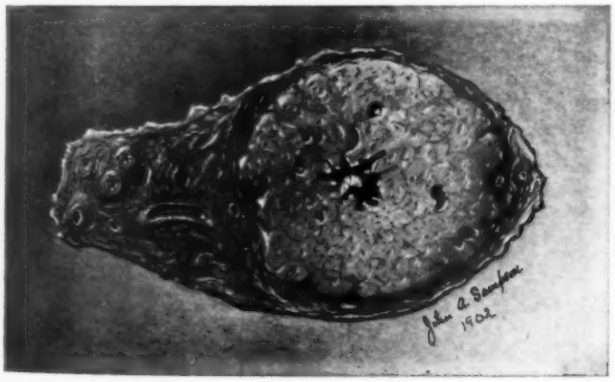

FIG. 2.—Gyn. No. 9860. Path. No. 6074. Natural size. Cross section, taken just below the level of the uterine artery, of a specimen from a hysterectomy for carcinoma of the cervix, where all the tissue between the cervix and pelvic wall, including the lower portion of the double ureter, was removed undisturbed, on the left side. On the right side the parametrium was cut through mesial to the ureter. The advantage gained by sacrificing the lower end of the ureter and removing undisturbed all the tissue lateral to the cervix, becomes very evident in comparing the two sides.

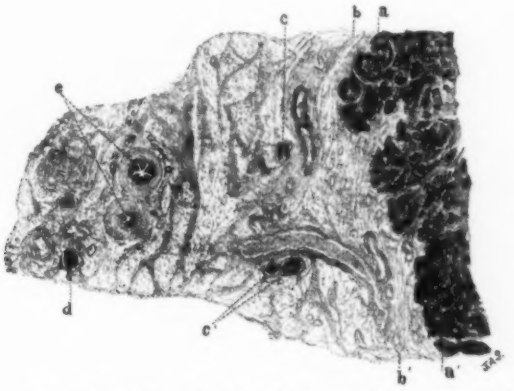

FIG. 3.—Section of the left parametrium, magnified twice, from specimen shown in Fig. 2.

a–*a'* is the outer border of the growth.

b–*b'* is the outer border of the cervix.

e is a cross section of the double ureter.

c–*c'* and *d* are small lymph nodes having a diameter from .5 to 1.5 mm.

In this section cancer was found in the node marked *d*, which is posterior and lateral to the ureter. In other sections cancer was found in a node situated near *c'*. In a less radical operation some of the nodes containing cancer would have been left behind.

the pressure of the growth on the ureters. By studying the reports of cases of radical operations for extensive carcinoma of the cervix, we are able to judge of the possibilities of such an operation. In these cases the evident extent of the disease is the indication for the operation. It seems to me that the indications for such an operation in the so-called favorable cases, are just as evident; namely—

1. The high percentage of recurrences.

2. The involvement of the pelvic glands, apparently in at least one-third of the operable cases.

3. The inability at operation to diagnose to what extent the surrounding tissues are involved by carcinoma.

In addition one must bear in mind that the most radical operation is probably indicated more in the early than in the very advanced cases, for in the former there is the greater chance for a cure. I have emphasized the importance of the more radical operation. I wish now to emphasize these facts:

1. That a more radical operation is very difficult and is attended with a higher primary mortality than a less radical one.

2. That such an operation is but in the experimental stage, and the question of the route to use, as well as whether it is best to resect the lower ends of the ureters in the early cases, and many other features in such an operation, are problems which have not been solved.

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NITROGEN EXCRETION IN PNEUMONIA, AND ITS RELATION TO RESOLUTION.[1]

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An unusually small number of crises and a large proportion of delays in resolution were occurring last fall in this Hospital, and several different methods of local treatment, such as ice bag and poultice to the chest were tried, with the view of shortening the course of the disease. Daily determinations of the total nitrogen excretion in each case by the Kjeldahl method were begun with the idea, that the daily surplus nitrogen excretion, above what would normally be excreted on the pneumonia diet, would be an index in direct proportion to the rapidity with which the involved lung was clearing.

This assumption was based: 1. Upon the fact observed by Svenson, Müller and others, that a post-critical nitrogen determination showed very marked increase in total daily nitrogen excretion, one case mentioned by Müller showing 28 grammes of nitrogen over what would normally be excreted on the same diet. This, as he took it, represented 175 grammes of albumin or 800 grammes of pneumonic exudate which had been absorbed by the blood from the involved lung, and finally found its way into the urine. This hypothesis our observations have tended to confirm. 2. Upon our idea as to the course of events in consolidation and resolution of pneumonic lungs as drawn from standard pathologies. This may be briefly stated as follows:

The lung first becomes congested, or, as it is termed, engorged. This is followed sooner or later by consolidation, first in the form of red, and later of grey hepatization. The lung is now firm and solid, weighing from 1000 to 1500 grammes, according to Bollinger, or even 2000 grammes, according to Osler, more than it did in the normal state. This 1000 to 2000 grammes of exudate in favorable cases, softens and is gradually absorbed, finally leaving the lung clear.

Thus, supposing that the exudate absorbed by the circulation would appear in the urine as some nitrogenous extractive, and believing there were approximately 500 to 1000 grammes of exudate per lobe to be accounted for in this way,

[1] Read before the Johns Hopkins Hospital Medical Society, June 2, 1902.

it is evident that by knowing how much nitrogen was excreted daily above the normal for existing conditions, and also how much pneumonic exudate one gramme of nitrogen represented, we might easily estimate what proportion of the exudate was being excreted each day.

The variations in nitrogen content of the fæces were not considered, as the total daily nitrogen excretion from this source only averages about two or three grammes, according to the statistics of Riess, while the comparatively small amount of sputum relative to pneumonic exudate allowed of its being disregarded likewise.

It was hoped that one local application might cause the expected amount of nitrogen to be excreted sooner than another, indicating a more favorable condition for rapid resolution.

It was soon found, however, that while this calculation did very well for the small proportion of cases that resolved quickly (Charts No. I and IV) say in three or four days, that in cases of delayed resolution (Charts No. II and VII) quite as large an amount was excreted daily without seeming to make any impression on the condition of consolidation as shown by physical signs. In other words, whereas the quickly resolving case excreted its expected 1000 or 2000 grammes of exudate in three or four days, leaving the lung clear, on the other hand, the slowly resolving case would excrete its surplus of 200 to 500 grammes daily day after day and even week after week and still retain a flat note over the involved lung.

This of course made it out of the question that the daily nitrogen determinations would be even the most distant index of the rate of clearing. The determinations were continued however in view of the interesting questions they suggested and I report them here, without reference to the question of treatment for which they were undertaken, and which will be reported later. I wish to express my great appreciation of the interest and kindness of Dr. Emerson with whose encouragement this work was undertaken, and whose invaluable assistance in the nitrogen determinations made its completion possible.

Twenty-two cases in all were followed, the figures of which I append in full. All were from the men's wards. Determinations in all the cases, for one reason or another, could not be made daily through their whole course, but those that are incomplete agreed for the days they could be followed with the ones observed from onset to recovery. Thus, though some are incomplete, they are valuable as controls and supplements for the rest.

I was especially fortunate in obtaining two cases from the initial chill on, and the others included four crises, four cases of marked delay in resolution, two with continued fever, and two afebrile after the tenth day.

One case ended in empyema, and one case died. Several cases showed successive involvement of two or more lobes. The number of lobes involved varied from one to four, and period of resolution from three days to eight weeks.

These patients took about 6 to 8 grammes of nitrogen a day in the routine milk and albumin-water diet during the continuation of the fever, and after the temperature became normal about 10 grammes of nitrogen in the general soft diet. Other patients than the pneumonia cases excreted about 8 grammes of nitrogen daily with a milk and albumin diet and 9 or 10 grammes of nitrogen with a soft diet.

The question may be asked, can the surplus nitrogen excretion in these cases be considered as representing in greater part pneumonic exudate, as Svenson and Müller surmised, and as our observations tend to confirm; or is it to be accounted for merely by the fever, or by the leucocytosis? Against the latter view are opposed the following:

1. Although the results of various investigators tend to show an increased metabolism as indicated by increased nitrogen excretion in many cases with pyrexia, some of the results are conflicting, and although it is undoubtedly true that in many cases pyrexia and increased nitrogen excretion are coincident, yet these cases (Charts I and III) show definitely that a continued fever of 104 degrees, accompanied by a leucocytosis of 20,000, may persist for several days consecutively, with the patient excreting a normal or subnormal amount of nitrogen; and also that for weeks after both temperature and leucocytes are normal a surplus of ten to fifteen grammes of nitrogen may be excreted daily (Charts II and VII). The interesting experiments of Krehl and Matthes[2] on aseptic fevers in man and animals, also show conclusively that it is not the temperature *per se* that causes the increase in metabolism and increased nitrogen excretion. They found that injections of certain poisons, such as iodine, silver nitrate and albumoses, may cause a rise in temperature or may not; but, in either case, the nitrogen output was increased, showing that it is the poisoning and not the temperature that causes the surplus nitrogen.

Again, the statistics of Riess[3] on nitrogen excretion in typhoid show one case that on the ninth and tenth days of the disease excreted an average of 16.4 grammes of nitrogen each day with a maximum temperature of 104.7°, and yet on the sixteenth and seventeenth day of disease passed an average of 16.5 grammes of nitrogen with a temperature of 100.2°, thus showing a difference of only one-tenth gramme of nitrogen with a difference in temperature of 4.5°. This same case on the twelfth and thirteenth days of the disease under treatment with continued bath passed twenty-three grammes of nitrogen per day, with an average temperature of 101.5°, thus treatment with hydrotherapy causes a difference of seven grammes of nitrogen per day, whereas 4.5 degrees of temperature caused but one-tenth gramme difference. So although pyrexia and leucocytosis may be accompanied by increased nitrogen output, no inevitable association nor causal relation can be considered proven.

2. In a pneumonia case with one lobe involved we know that 500 to 1000 grammes of exudate must be gotten rid of in some way and our observations on two cases in which a single lobe resolved in several days showed during those days

[2] Archiv f. Ex. Path., vol. 40.
[3] Archiv f. Ex. Path., vol. 22, p. 151.

a total surplus nitrogen excretion of 440 grammes and 1070 grammes respectively. This leaves but little to be accounted for by either fever, leucocytosis or toxæmia.

3. The surplus nitrogen, although showing no definite relation to the temperature, does show a very close coincidence with physical signs, that is after resolution once begins. Thus we find that after the first few days, whenever the lung by clinical signs shows consolidation, we get surplus nitrogen, and as soon as these signs are clear we have normal nitrogen excretion.

The history of a pneumonia case from the point of view of nitrogen excretion seems to be as follows:

During the first day or so following the initial chill the nitrogen output is below normal, as we might expect when we consider that is short while 500 to 1000 grammes of exudate per lobe is stored in the involved lung at the expense of the rest of the body. It is in this way that Bollinger explained the oligæmia to which he called attention in pneumonia.

From about the third day on we find a gradual rise in nitrogen excretion corresponding, as I interpret it, in greater part, to beginning resolution and absorption of the liquefying exudate, plus probably some excretion of destroyed tissues retained in other parts of the body. This finally comes to a maximum in two more days, and if there is no further involvement, and the lung is clearing well, the nitrogen excretion returns rapidly to normal.

There are variations from the above picture of what may be taken as a type of the average favorable case.

In one case evidences of beginning resolution did not come until the sixth day. This was an old man of sixty with an alcoholic history (Case 3). In another (Case 12) the rise in nitrogen output came on the second day with involvement of a second lobe. This was after one day's interval without fever, physical signs, or surplus nitrogen. In other words, the patient was well for one day, then suffered involvement of the opposite lower lobe which began to resolve on second day, and was practically clear and the patient well on the sixth day.

The greatest variations are found in time required for resolution, one case requiring three, another six, and a third over eight weeks.

It was in such cases of delayed resolution that the remarkable quantity of surplus nitrogen was excreted. One case (See Chart II, Case 16) during the first thirteen days of admission excreted a surplus amount of nitrogen which would represent the weight of exudate in four consolidated lungs, yet this patient's lung was not entirely clear on the twenty-fourth day of admission, and but one lobe of one lung was ever involved. Tempeature had been normal since the eighth day.

A second case (Case 5) also excreted the equivalent of four consolidated lungs, and this during the first twenty-four days of admission, and the chest had not cleared on the sixtieth day, and in this case but one lung was ever involved, and the temperature had been normal since the seventeenth day. Several other of the cases during delay in resolution excreted much more nitrogen than could be accounted for by the original quantity of exudate. To account for this brings us back to the same difficulty that made the nitrogen determinations useless as an index to the rate with which the lung was clearing. Now if, as we believe, the total surplus nitrogen in these cases still represents, in great part, absorbed pneumonic exudate, and exceeds by many fold the original area of consolidation, the only supposition left tenable is, that the pulmonary condition in these cases is not, as we took for granted, a passive status quo, waiting for weeks to be carried away, but a continually progressing cycle of formation, liquefaction, and absorption of pneumonic exudate.

If we look at the question in the light of recent work that has been done by Müller[1] on resolution in pneumonia, it makes it all the more improbable that the hepatized lung should remain filled with the same consolidated exudate at the end of a couple of months as it had at first. He found that a lump of lung in the stage of grey hepatization, if rendered sterile to exclude bacterial action, and kept at the same temperature as the body, would resolve invariably and completely in a few days. This he showed was due to the presence of autolytic ferments derived probably from the cellular elements of the exudate.

Why should such a lung, if left in the body, remain unchanged? I cannot conceive that it could, except with the rather chimerical assumption of the formation of antiferments. Now if it does liquefy and does not clear, it must be because the liquid is retained in the lung. But we know this is not the case; for,

1. When such cases come to autopsy the lung is solid, as in the case Grissole described in which at autopsy on the 60th day the affected part showed a condition not unlike that of the acute stage. (Osler.)

2. We obtain the equivalent of that liquid several times over in the urinary excretion.

This, of course, throws no light upon the course of the symptomatic side of the picture, and only emphasizes the fact long recognized that the pulmonary condition bears no definite relation to the clinical symptoms. An explanation of defervescence and a drop in leucocytes with continued local conditions, must probably be postponed with many similar problems to the day when the conceptions of specific antibodies are elucidated.

The fact that many of these cases where the lung remains solid are afebrile and show no leucocytosis is no contraindication to a continued local process. For many other morbid conditions involving pus formation become afebrile and without leucocytosis after surgical interference or spontaneous evacuation, although the local inflammation, as evidenced by copious pus formation, continues. Then, besides, in pneumonia we so often see a patient with violent fever and rapid heart, and seemingly on the verge of dissolution, several hours later sleeping quietly, or asking for food, apparently well. It is scarcely conceivable that an inflammation which

[1] Verh. d. Naturforsch. Gesellsch. in Basel. Band XIII, Heft 2.

can produce 1000 or 2000 grammes of exudate in a couple of days, would come to a complete standstill in several hours.

The case ending in empyema is of special interest in that it suggests that nitrogen determination may be of diagnostic value in doubtful cases with continued flatness. In this case with a flat note over the left chest on the 17th day the nitrogen excretion was about normal, whereas in every case where a continued flat note was due to delayed resolution the nitrogen excretion was much above normal. The explanation of this would seem to lie in the different capacity of the pulmonary tree and the pleural sac for absorption.

In view of Müller's suggestion that the leucocytes might furnish a large part of the ferment concerned in the liquefaction of the exudate, I was interested in comparing the leucocytosis curve with that of the nitrogen excretion.

His supposition of the importance of the leucocytes in this process was drawn from the knowledge that pus does contain a proteid-splitting ferment, and from the microscopic picture of the stages of resolution. He pointed out that in the stage of grey hepatization where resolution first begins the microscopic picture shows an increase in leucocytes.

From another point of view I find an analogous phenomenon. The leucocytes in the blood reach their maximum a day or two before the maximum excretion of nitrogen; and in cases where the nitrogen output soon reaches normal the curve of leucocytosis follows it closely, though the temperature may have fallen a day or so previously.

The case mentioned above where increased nitrogen output did not appear until the seventh day, had, previous to that time a leucocytosis of about 17,000; on the second day after, with a nitrogen output which had increased 500 fold in three days, the leucocytosis was 28,000.

All of which tends to substantiate Müller's idea that the leucocytes play an important part in the process of resolution. That there is no leucocytosis during the latter part of many cases of delayed resolution is difficult of explanation, but not more so than the similar condition so frequent in surgical cases as mentioned above, where, after operation, a continued pus formation goes on after the leucocytes are normal.

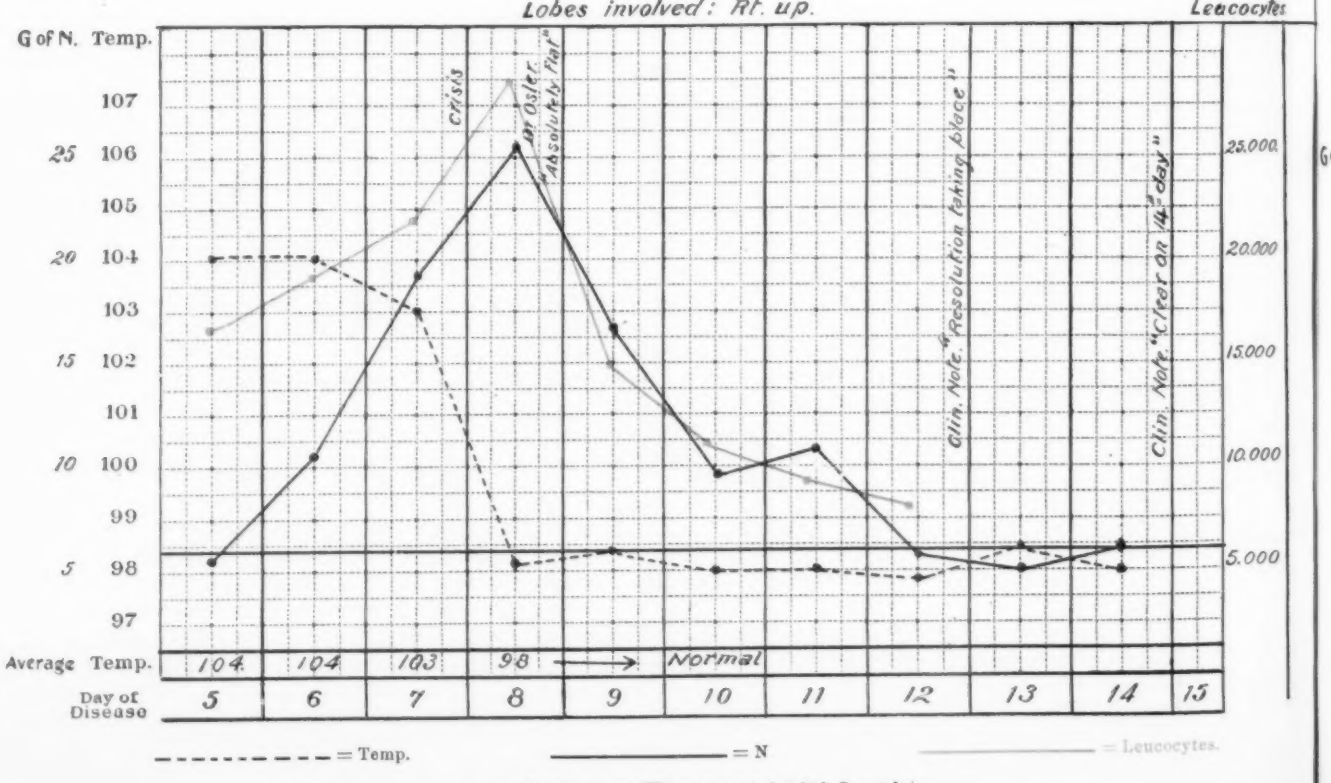
To sum up:

1. In cases of pneumonia a surplus amount of nitrogen must be excreted during the days of resolution that will correspond at the least to the original quantity of exudate poured into the involved lung. In most cases there is more, the rest representing in great part a continuation of the formation and an absorption of inflammatory exudation, plus other tissue destruction.

2. In cases of marked delay in resolution the continued high nitrogen output indicates a continuation of the local inflammatory process, so that in those cases of several months' persistence we might speak of a chronic pneumonia.

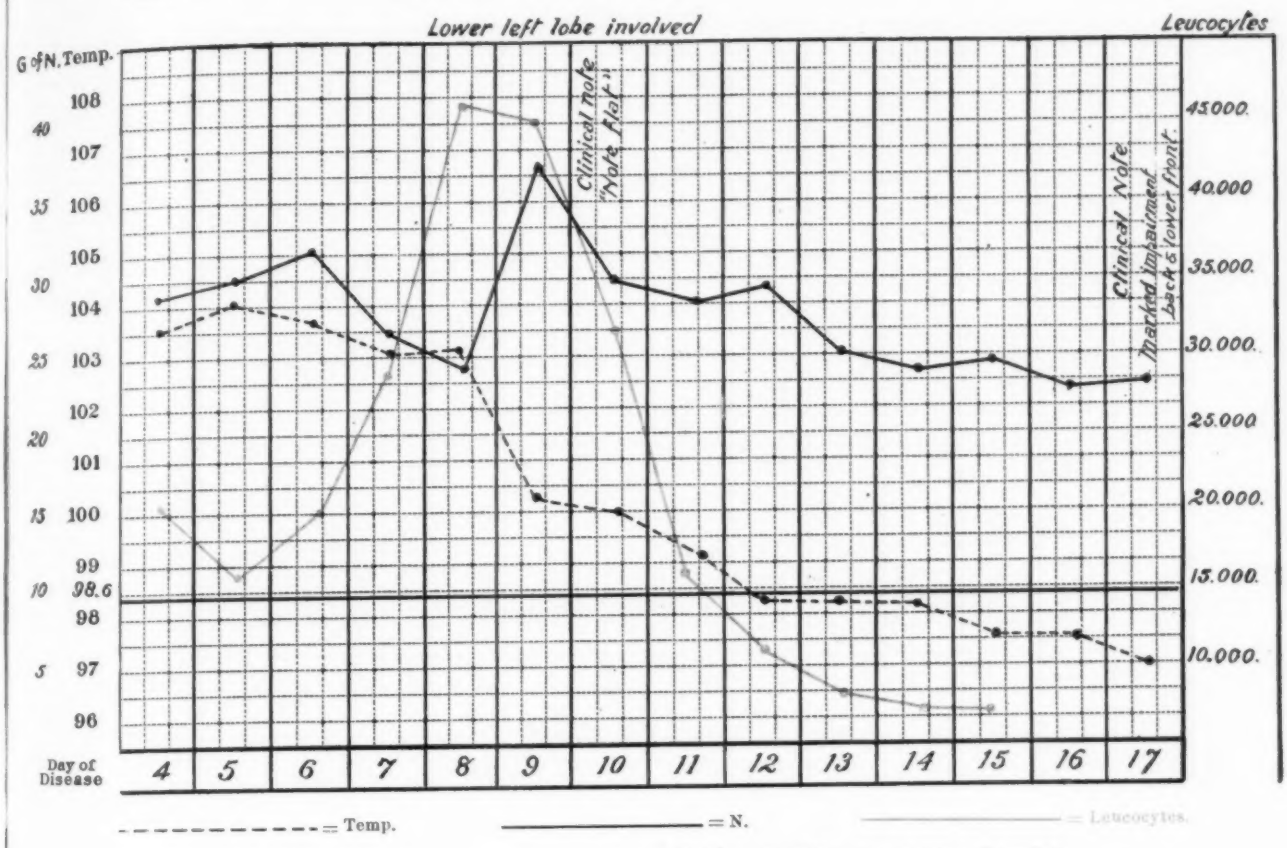
3. In cases of rapid resolution the leucocytosis curve follows the curve of nitrogen excretion with a very striking parallelism, and would seem to point to a causal relation between leucocytes and resolution.

CHART I. CRISIS WITH PROMPT RESOLUTION. CASE 3.



Total surplus N represented 1,540 G exudate.

CHART II. LYSIS WITH DELAYED RESOLUTION. CASE 16.



Not clear on 27th day.

Total surplus Nitrogen = 7,000 + G exudate.

CHART III. CRISIS WITH DELAYED RESOLUTION. CASE 2.

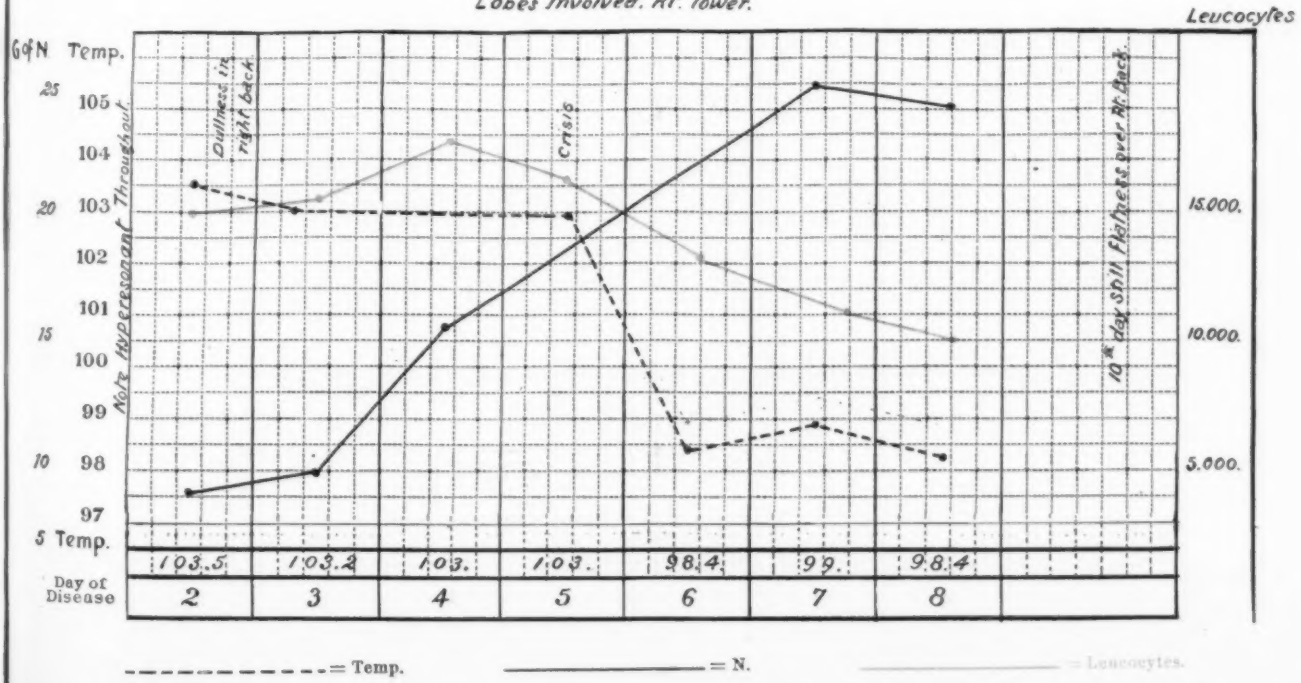
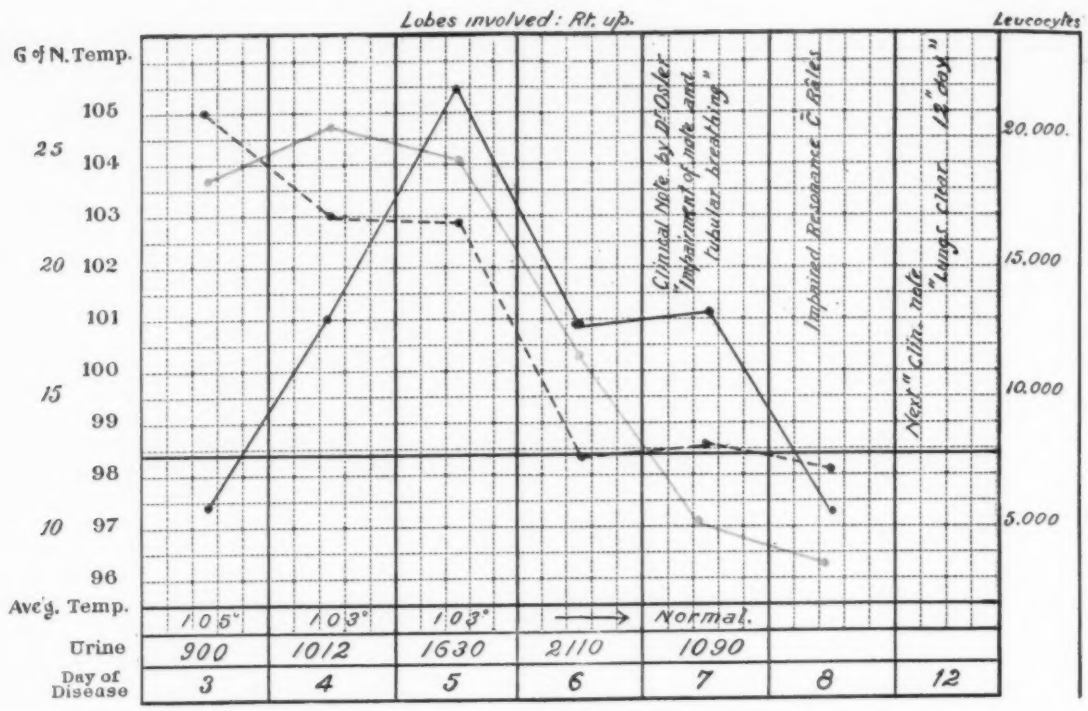


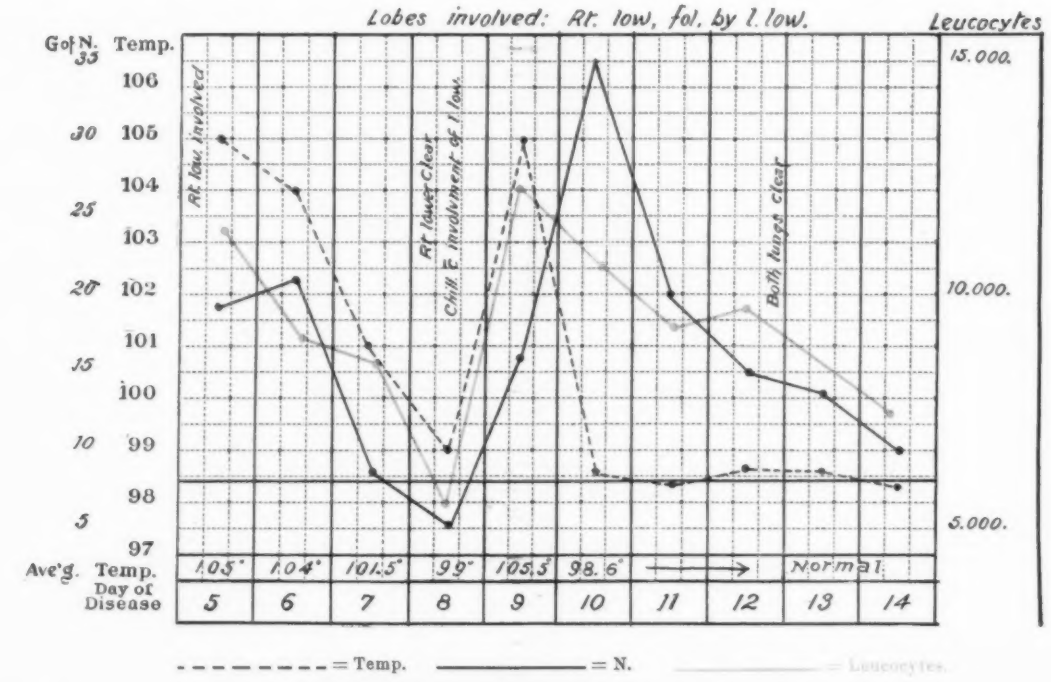
CHART IV. CRISIS WITH PROMPT RESOLUTION. CASE 18.



= Temp. = N. = Leucocytes.

Total surplus N represented 1,070 G of exudate.

CHART V CRISIS WITH PROMPT RESOLUTION. CASE 12.



= Temp. = N. = Leucocytes.

Nitrogen excretion for 2d lobe = 440 G exudate.

CHART VI. CRISIS WITH PROMPT RESOLUTION. CASE 14.

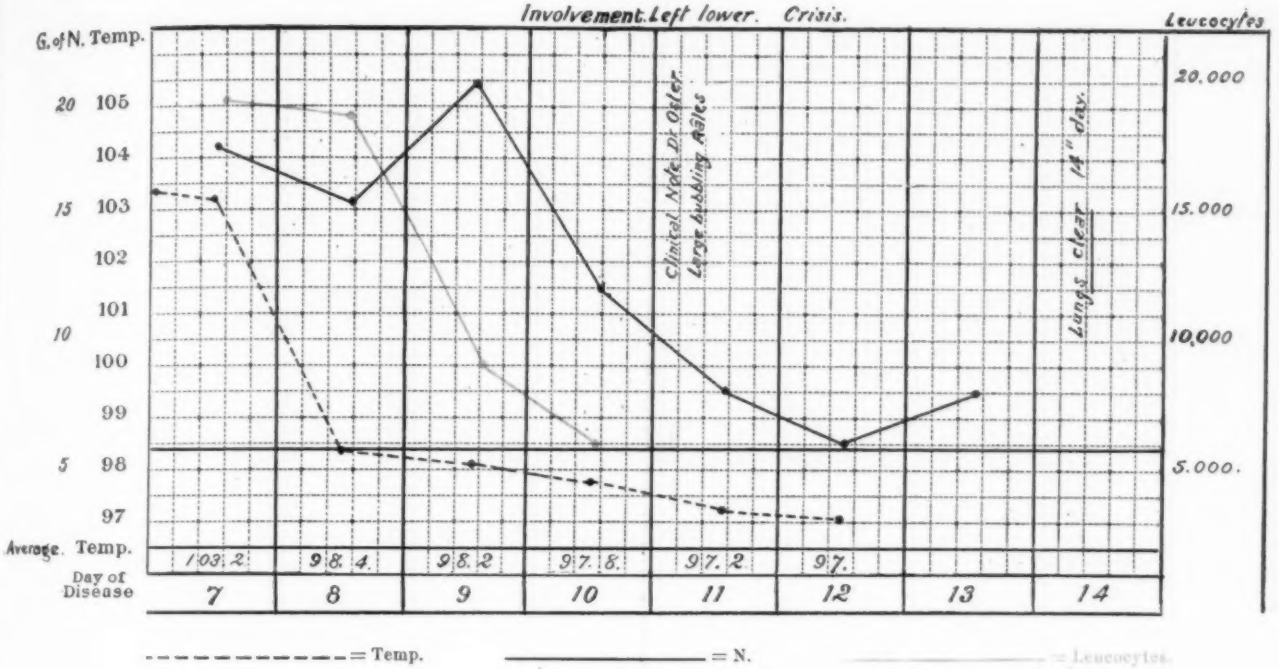
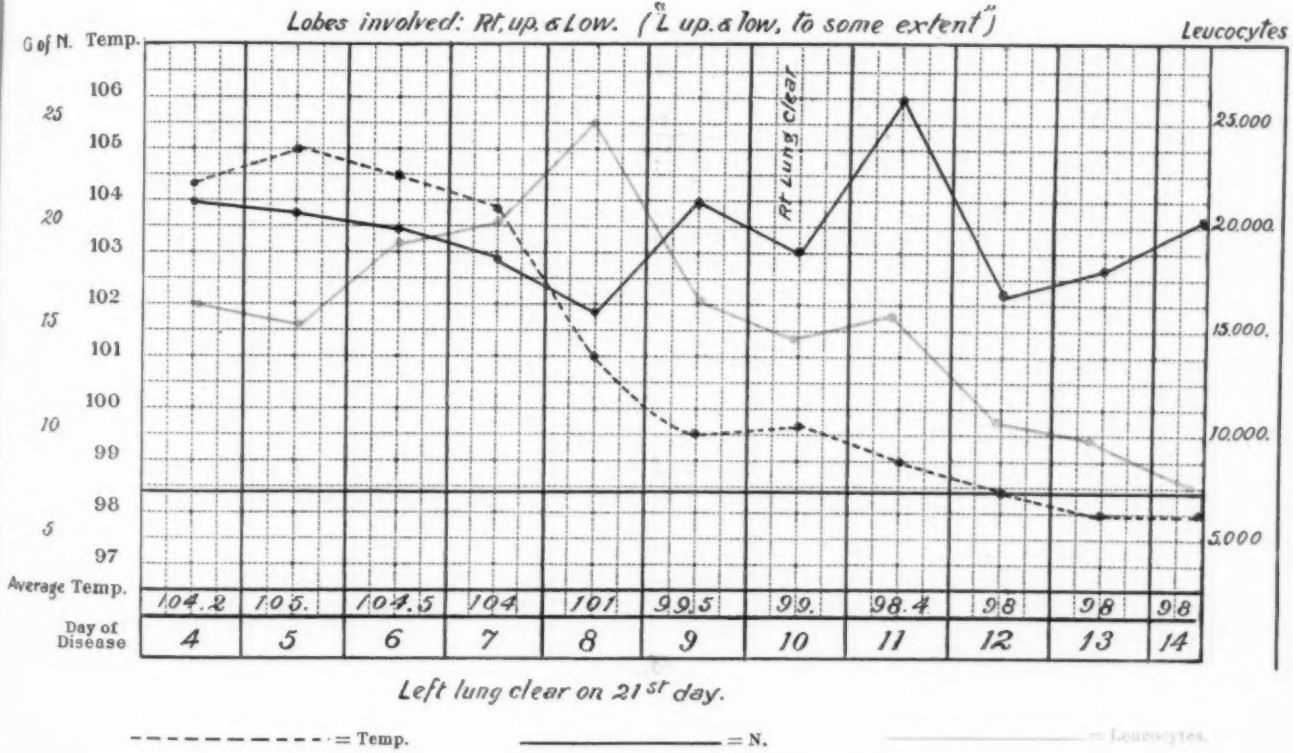


CHART VII. LYSIS WITH DELAYED RESOLUTION. CASE 1.



Total surplus N represented 2,600 G exudate, to 14th day.

CASE 1.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	4	1200	21.3	16,300
	5	1310	20.7	15,000
	6	1240	20.2	18,000
	7	1640	18.9	19,000
	8	1160	16.5	25,000
	9	1600	23.2	14,000
L. lung clear. Temp. normal.	10	920	18.6	15,000
	11	1440	27.8	....
	12	1280	15.5	11,000
	13	1110	16.2	....
	14	1070	19.5	8,000

This was a very severe case of lysis with both lungs involved on admission. Resolution was slightly delayed. Lungs clear by physical signs on the 21st day. Total surplus N to 14th day represented 2.600 G exudate. See Chart VII.

CASE 2.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
Dullness in rt. back	2	540	9.5	15,000
	3	550	9.8	15,700
	4	840	15.6	18,000
Crisis	5	1060	17.0	1.,000
	6	1660	....	13,900
	7	3240	24.9	12,500
	8	2175	23.2	10,000

Crisis with delayed resolution. On admission, 1st day of disease, note was hyper-resonant throughout chest. On 2nd day dullness in rt. back. On 10th day still flatness in rt. back. Clear on 23rd day. Involv. rt. lower. See Chart III.

CASE 3.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	5	320	5.5	17,000
	6	460	10.6	19,000
Crisis	7	1050	19.8	22,000
	8	1380	25 6	28,000
	9	1140	17.2	15,000
	10	1440	9.8	10,000
	11	1660	13.8	9,000
	12	750	5.8	8,000
	13	....	....	....
	14	....	....	....
	15	1000	5.4	....
	16	1140	6.3	....

Crisis with prompt resolution. Almost entirely clear on 13th day. Involvment rt. upper. See Chart I.

CASE 4.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	3	780	11.2	13,000
	4	930	12.3	14,000
	5	670	9.6	22,000
	6	680	10.2	25,000
	7	610	19.9	21,000
	8	1060	15.2	28,000
	9	1040	21.1	23,000
	10	1520	....	....
	11	1280	12.5	22,000
	12	790	11.2	13,000
Temp. nor.....	13	1020	13.1	19,000
	14	890	12.2	....
	15	965	....	....
	16	920	....	....
	17	1030	....	....
	18	780	11.2	...
	19	1290	11.5	....
	20	1380	....	....
	21	580	9.2	....
	22	985	10.1	....
	23	660	....	15,000
	24	780	13.1	13,000
	25	1230	16.6	....
	26	640	....	12,000
	27	970	14.2	....
	28	....	....	9,000

Lysis with delay in resolution. Clear on 31st day.
Involv.—Left lower; later right lower.

CASE 5.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	4	1000	8.5	26,000
	5	1040	11.5	....
	6	1040	....	6,000
	7	1500	21.0	8,700
	8	1860	29.6	14,100
	9	2440	37.5	22,000
	10	2135	36.3	17,000
	11	1670	32.0	....
	12	1620	26.5	18,000
	13	2200	32.8	15,700
	14	1620	24.1	10,600
	15	1440	21.2	....
	16	1450	21.3	....
	17	1450	24.6	....
Temp. nor.....	18	1180	20.6	10,000
	19	2620	22.0	....
	20	1960	19.3	5,400
	21	1360	17.1	5,000
	22	1220	12.9	8,100
	23	1460	17.4	....
	24	1180	15.9	....
	25	1330	18.1	....
	26	1320	15.9	....
	27	1890	15.2	....

Lysis with marked delay in resolution. Not quite clear on 60th day.
Involv.—Left lower and upper. Surplus N excretion for 23 days represented 7,400 G exudate.

CASE 6.

Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
4	720	25.2	8,000
5	1260	27.5	5,000
6	1150	22.6	9,000
7	1080	24.1	12,000
8	1310	27.1	....
9	1520	28.2	13,000
10	980	19.5	11,000
11	900	18.7	....
12	1100	20.5	11,000
13	....	....	....
14	910	17.1	14,000
15	800	15.3	14,000
16	630	14.1	....
17	420	9.5	14,000
18	930	8.1	....

Case ending in empyema. Pus drawn on 19th day.
It is noteworthy that with the side flat on 17th day there was approximately a normal N excretion. Involv. l. lower.

CASE 7.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	4	1600	26.8	15,000
	5	1500	25.4	8,000
	6	2220	35.7	5,000
Involv. of low. lobe.....	7	880	15.8	....
	8	1160	22.7	6,000
	9	2720	28.6	10,000
	10	2790	15.4	11,000
Up. lobe clearing	11	1020	9.6	13,000
	12	1180	11.7	9,000
	13	1800	25.5	9,000
	14	2340	30.7	9,000
	15	2400	25.5	8,000
	16	1860	26.0	7,500
	17	1800	42.4	....
	18	1660	19.7	....
	19	1140	14.9	....
	20	1320	16.6	....
	21	1520	17.0	....
	22	1000	10.0	....

Severe case, ending by lysis on 10th day. Resolution delayed. Not entirely clear on 25th day. Rt. up. involved on admission, clearing on 12th day. Rt. low. involved about 7th or 8th day.

The rise and decline in N excretion corresponding to the successive clearing and involvement of the two lobes is well shown. Surplus N represents 6000+G exudate.

CASE 8.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	6	1185	23.2	10,000
	7	1140	19.7	....
	8	1240	22.9	37,000
	9	1245	23.2	40,000
	10	1105	25.1	18,000
	11	775	23.9	20,000
	12	770	18.6	16,000
Temp. nor	13	780	15.1	....
	14	670	14.2	....
	15	....	....	12,000
	16	....	....	9,000

Lysis with only slight delay in resolution. Clear on 15th day. Involvement: Left upper and lower lobes.

CASE 9.

Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
4	500	9.3	25,000
5	1080	21.8	20,000
6	1400	28.9	30.000
7	1260	22.1	31,000

Death on 8th day. From the increase in N excretion it would appear that absorption had been taking place since 5th day. Involvement: Right upper and lower lobes.

CASE 10.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
Crisis	5	1120	18.2	10,000
	6	840	18.4	7,000
	7	860	19.7	4,500
	8	905	19.2	5,000
	9	630	13.4	....

Crisis with slight delay in resolution. Clear on 14th day. Involvement: Left lower.

CASE 11.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	3	920	14.9	13,650
	4	1170	....	10,700
	5	1270	23.5	....
	6	1200	27.2	....
	7	1240	28.9	8,000
Temp. nor.....	8	860	19.0	....
	9	940	20.1	10,000

Lysis with delayed resolution, not quite clear when discharged on 20th day. Involvement: Left lower.

CASE 12.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	5	1372	19.1	11,600
	6	1500	20.0	8,200
Rt. lung clear. Chill with involv. of l. lung.....	7	1320	7.02	8,000
Signs at l. base.	8	1130	5.5	5,500
	9	1440	16.0	12,100
	10	880	16.3	10,500
	11	1820	35.6	9,000
	12	1506	20.0	10,000
	13	1250	15.31	6,000
Clear.....	14	1520	14.3	....
	15	1380	10.0	....

Successive involvement of two different lobes, first terminating by lysis, second by crisis, both resolving promptly. See Chart V.

CASE 13.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	5	1160	25.4	12,600
	6	1500	36.4	6,000
	7	1340	31.4	7,000
	8	1380	31.5	6,000
	9	1370	32.6	....
	10	1090	29.0	....
	11	960	18.9	....
Temp. nor.....	12	....	....	....

Lysis with some delay in resolution. Clear on 15th day.
Involv.—Rt. up. and low.

CASE 14.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	7	900	18.2	19,000
Crisis	8	760	15.3	18,700
	9	1000	21.9	9,000
	10	560	11.5	6,000
	11	470	7.1	....
	12	400	7.6	....
	13	410	6.7	....

Crisis with prompt resolution. See Chart VI.
Involv.—L. lower.

CASE 15.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
Fall in temp. began.....	7	2000	26.3	24,800
	8	2010	23.2	24,000
	9	1860	21.5	16,300
	10	1160	16.2	23,200
Temp. nor.....	11	1640	18.8	19,100
	12	1340	15.2	18,800

Lysis with moderate delay in resolution. Clear on 15th day.
Involv.—Rt. upper.

CASE 16.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	4	1470	28.1	20,000
	5	2160	30.2	15,000
	6	1960	32.9	17,000
	7	1680	26.6	28,000
	8	1560	24.8	45,000
	9	2625	37.3	44,000
Temp. nor.....	10	2380	30.8	30,000
	11	2460	28.6	14,000
	12	2190	29.3	8,000
	13	1840	25.6	10,000
	14	1220	23.7	7,000
	15	1400	24.0	7,000
	16	1420	24.2	....
	17	1070	23.2	Normal.
	18	1050	23.5	

Lysis with delayed resolution. Not entirely clear on 28th day.

Involvement.—Left lower. Surplus N from 4th to 18th day represented 7,100 G exudate. See Chart II.

CASE 17.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes
	5	1400	19.0	14,000
	6	1460	23.6	16,000
	7	2060	33.4	11,250
	8	2050	26.9	....
	9	1750	23.1	23,000
	10	1690	23.6	18,500
	11	2340	23.4	12,000
	12	2460	31.5	15,600
	13	2510	14.3	16,200
	14	3205	14.3	5,830
	15	2290	17.6	....
	16	1490	15.6	12,000
	17	1305	16.6	15,000
	18	1230	. .	9,500
Temp. nor.....	19	1160	19.1	8,200

Lysis with marked delay in resolution. Not clear until 48th day.

Involvement.—Whole of left lung, and right lung to slight degree.

CASE 18.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	3	900	11.3	18,000
	4	1020	17.9	20,000
Crisis	5	1630	26.9	19,000
	6	2010	17.7	11,000
	7	1090	18.6	3,000
	8	770	11.9	4,000

Crisis with prompt resolution. Perfectly clear on 12th day. See Chart IV. Involvement.—Rt. up. lobe.

CASE 19.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	3	2290	10.8	15,000
	4	....	....	21,000
	5	2090	12.0	15,000
	6	1400	20.9	....
Temp. nom.....	7	1180	16.5	14,000
	8	960	14.5	....
	9	820	13.2	15,000

Lysis with slight delay in resolution. Clear on 16th day.

Involv.—Left lower.

CASE 20.

	Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
	6	1640	17.9	19,000
	7	1680	19.6	18,000
	8	1780	37.1	20,000
Temp. nor.....	9	1780	26.1	21,000
	10	1150	17.5	21,000
	11	1150	20.5	....
	12	1050	19.3	18,000
	13	990	19.4	12,000
	14	1140	19.7	....
	15	810	....	10,000
	16	800	13.5	....
	17	740	10.4	....

Lysis with slight delay in resolution. Clear on 18th day.

Involv.—Rt. and left lower lobes.

Two incomplete cases.

CASE 21.

Day of disease.	Cc. urine in 24 hours.	G of N in 24 hrs. urine.	Leucocytes.
5	1190	9.7	11,000
6	760	12.6	8,000

Lysis with prompt resolution. Clear on 12th day.

Involv.—Rt. up.

CASE 22.

7	1780	19.1	15,000
8	1270	37.9	14,000
9	1170	31.0	21,000

Lysis with slight delay in resolution. Clear on 15th day. Temp. normal on 13th day.

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